

Article

The Association Between *TGFB1* and *PDGFA* Gene Variants and Non-Contact Knee Ligament Rupture Risk in Professional Handball Players

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Abstract

Ligament injuries are common among athletes and are influenced by both environmental and genetic factors. Growth factor signaling plays a central role in fibroblast proliferation, extracellular matrix remodeling, tissue regeneration, and ligament healing. However, the contribution of genetic variants in *TGFB1* and *PDGFA* to susceptibility to non-contact knee ligament rupture (NCKLR) remains unclear. This exploratory case–control study investigated the association of *TGFB1* (rs1800470, rs1800469) and *PDGFA* (rs1800814, rs2070958, rs62433334) polymorphisms, as well as *PDGFA* haplotypes and gene–gene interactions, with NCKLR risk in elite handball players. The study included 331 elite athletes, comprising 102 players with a history of NCKLR and 229 uninjured controls. Genotyping was performed using Real-Time PCR, followed by single-locus, haplotype, and multifactor dimensionality reduction (MDR) analyses. FDR correction was applied for multiple comparisons. No significant associations were observed for the investigated *TGFB1* variants. In contrast, *PDGFA* rs2070958 was associated with NCKLR status in the recessive model (OR = 2.00; 95% CI 1.16–3.46; $p = 0.01$); because rs2070958 deviated from Hardy–Weinberg equilibrium in the total sample and in the NCKLR group, but not in controls, this finding should be interpreted cautiously. The A allele of rs1800814 was associated with reduced injury odds (OR = 0.60; 95% CI 0.42–0.85; $p = 0.004$). Significant associations were also identified for the *PDGFA* A-T-G haplotype and for an MDR model involving *TGFB1* rs1800469, *PDGFA* rs1800814, and *PDGFA* rs2070958. These findings suggest that *PDGFA* genetic variability may be associated with NCKLR status, whereas no evidence of association was observed for the *TGFB1* polymorphisms investigated.

Keywords: ligament rupture; single-nucleotide polymorphism; transforming growth factor beta 1; platelet-derived growth factor A



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1. Introduction

Ligament injuries are among the most common musculoskeletal injuries in athletes and represent a major cause of time loss from training and competition [1]. In handball, frequent rapid accelerations, changes in direction, jumping, and player-to-player contact contribute to a high incidence of lower limb injuries, particularly those involving the knee joint [2]. Greater cumulative exposure to intensive training and competition may contribute to tissue fatigue and the accumulation of microdamage in soft connective tissues such as tendons and ligaments. If repetitive loading exceeds the adaptive and reparative capacity of the tissue, it may disturb extracellular matrix homeostasis and lead to progressive tissue degeneration, thereby increasing susceptibility to overuse injuries [3–5]. Non-contact injuries of the anterior cruciate ligament (ACL) and other knee ligaments are particularly important due to their prolonged rehabilitation, high risk of recurrence, and potential long-term consequences for athletic performance and joint stability [6,7]. The risk of non-contact knee ligament rupture is multifactorial and reflects the interaction of intrinsic and extrinsic factors rather than a single biological determinant. Biomechanical and neuromuscular parameters, such as knee valgus loading, knee flexion angle, trunk position, and muscle activation patterns, have been linked with non-contact ACL injury risk [8,9]. Sex is another relevant intrinsic factor. In handball, anterior cruciate ligament injuries have been reported more frequently among female players than male players. This occurrence may be related to interacting neuromuscular, biomechanical, anatomical and hormonal factors [10]. Previous injury history is another important factor that should be considered. Prior ACL injury may alter neuromuscular control, movement strategy, proprioception, limb symmetry, psychological readiness, and tissue tolerance, potentially increasing susceptibility to subsequent injury [11,12]. Previous studies have shown that injury risk may differ between match and training exposure [13], and that higher competitive level may be associated with greater ACL injury incidence in professional handball players [12]. Surface friction and traction characteristics may also influence knee loading during landing, cutting, and pivoting movements [14]. Although ligament injuries are multifactorial and strongly influenced by environmental factors, accumulating evidence suggests that genetic predisposition may contribute to connective tissue structure, mechanical properties, and overall susceptibility to musculoskeletal injury [15–17]. Genetic variation should be considered as one potential component of a broader multifactorial injury risk, potentially influencing connective tissue properties, extracellular matrix remodeling, and adaptive responses to repeated mechanical loading [18]. Several candidate genes have been proposed to influence susceptibility to tendon and ligament injuries, particularly those involved in collagen organization, extracellular matrix homeostasis, inflammatory signaling, and connective tissue adaptation [17,19,20]. Growth factor signaling plays an important role in connective tissue biology by regulating fibroblast activity, collagen synthesis, extracellular matrix organization, and responses to mechanical loading [21,22]. Among the growth factors implicated in these processes, transforming growth factor beta (TGF- β) [23] and platelet-derived growth factor (PDGF) are important regulators of connective tissue healing and remodeling [24]. TGF- β signaling regulates collagen synthesis and extracellular matrix remodeling [25,26], and PDGF promotes fibroblast proliferation, cellular migration, and matrix synthesis [27,28]. Consequently, genetic variability within genes encoding these growth factors may influence connective tissue properties and susceptibility to musculoskeletal injuries. Identification of genetic factors associated with injury susceptibility may contribute to future multifactorial models of injury risk assessment and athlete monitoring programs. Despite the recognized roles of TGF- β and PDGF signaling in connective tissue biology, few studies have examined whether genetic variability in *TGFB1* and *PDGFA* contributes to susceptibility to ligament injuries in athletes. Moreover, evidence regarding associations between *TGFB1* and *PDGFA*

polymorphisms and non-contact knee ligament ruptures (NCKLR) in elite handball players remains limited. *TGFB1* variants, including rs1800470 and rs1800469, have been reported to influence TGF- β 1 expression or activity and have been investigated in various pathological conditions involving inflammation, fibrosis, and extracellular matrix regulation [29,30]. Additionally, *TGFB1* rs1800469 has previously been examined in relation to Achilles tendon pathology [31]. The investigated *PDGFA* polymorphisms were selected because of the biological role of PDGF signaling in fibroblast proliferation and extracellular matrix synthesis, although its role in ligament injury susceptibility remains poorly understood. Because individual SNP (single-nucleotide polymorphism) analyses may not fully capture the combined effects of linked variants, haplotype analysis was also performed to assess allele combinations that may reflect local interactions among polymorphisms [32]. Furthermore, interactions between variants located in different genes may influence biological pathways involved in connective tissue remodeling and injury susceptibility. Therefore, both haplotype analyses and multifactor dimensionality reduction (MDR) analyses of potential gene–gene interactions were included in the present study. Because *TGFB1* and *PDGFA* are involved in connective tissue remodeling and healing, polymorphisms within these genes represent biologically plausible candidates for studies of ligament injury susceptibility. Accordingly, this study aimed to investigate the association between *TGFB1* polymorphisms rs1800470 and rs1800469 and *PDGFA* polymorphisms rs1800814, rs2070958, and rs62433334, as well as *PDGFA* haplotypes and potential *TGFB1*–*PDGFA* gene–gene interactions, with the risk of NCKLR in elite Caucasian handball players competing in the highest tier of professional handball. We hypothesized that *TGFB1* and *PDGFA* polymorphisms, both individually and in combination as haplotypes and multi-locus interactions, would be associated with susceptibility to NCKLR in elite handball players.

2. Materials and Methods

2.1. Participants

The study included 331 elite handball players competing in the Polish SuperLiga, the highest level of professional handball competition in Poland. The cohort comprised 127 women (age 23.5 ± 4.53 years; BMI 23.42 ± 2.27 ; body fat percentage $21.29\% \pm 4.61\%$) and 204 men (age 24.11 ± 5.11 years; BMI 26.28 ± 2.67 ; body fat percentage $14.20\% \pm 4.22\%$). The injury group (NCKLR) consisted of 102 elite handball players (51 women and 51 men). Inclusion criteria for the injury group were: age between 18 and 30 years, active participation in professional handball competition, and a history of at least one NCKLR. In the present study, NCKLR was defined as any self-reported non-contact rupture of the major knee ligament structures, including the anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), lateral collateral ligament (LCL), medial collateral ligament (MCL), and patellar ligament (PL). Eligible injuries included rupture of the ACL ($n = 68$, including 35 men and 33 women), PCL ($n = 6$, 5 men and 1 woman), LCL ($n = 15$, 5 men and 10 women), MCL ($n = 8$, 4 men and 4 women), or PL ($n = 18$, 3 men and 15 women). Players with contact-related knee injuries were excluded from the study group.

The control group comprised 229 elite handball players, including 76 women (age 22.73 ± 4.45 years; BMI 23.61 ± 2.51 kg/m²; body fat percentage $21.55\% \pm 4.86\%$) and 153 men (age 23.75 ± 4.92 years; BMI 26.31 ± 2.63 kg/m²; body fat percentage $14.35\% \pm 4.27\%$). Participants were professional Polish SuperLiga players recruited from the same competitive level and, where possible, from the same clubs as athletes in the NCKLR group. Control athletes did not differ substantially from injured athletes in terms of training experience. Eligibility criteria included active participation in professional handball competition and no history of knee ligament rupture. Athletes with any previous knee ligament rupture, regardless of the injury mechanism, were excluded from the control

group. Participants from both groups were exposed to comparable training loads. The questionnaire included information on training experience, number of training sessions per week, duration of a single training session, history of knee ligament rupture, number of knee ligament injuries, ligament injury grade, diagnostic method used to confirm the injury, description of the injury mechanism, previous ligament injuries outside the knee joint in the lower limb, history of rheumatological diseases, and history of medication use, particularly steroid treatment.

Medical and training history data were collected using a standardized questionnaire. Body composition parameters were assessed using the TANITA MC-780 analyzer (Tanita Corporation, Tokyo, Japan).

2.2. DNA Extraction

Buccal cells were collected by using Copan FLOQSwabs (Copan Diagnostics, Inc., Murrieta, CA, USA). DNA extraction was performed with the High Pure PCR Template Preparation Kit (Roche Diagnostics, Munich, Germany) according to the manufacturer's protocol. The quality of the obtained genetic material was measured using a NanoPhotometer NP80 spectrophotometer (Implen, Munich, Germany). No sample was excluded from the study because of poor DNA quality.

2.3. Genotyping Analyses

Genotyping was performed using Real-Time PCR on a QuantStudio 1 Real-Time PCR thermal cycler (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) with TaqMan probes detecting SNPs (TaqMan Assays and TaqPath ProAmp Master Mix, Thermo Fisher Scientific, Waltham, MA, USA). The study included probes *TGFB1* rs1800470 A/G (C__22272997_10), *TGFB1* rs1800469 A/G (C__8708473_10), *PDGFA* rs1800814 A/G (C__64631795_10), *PDGFA* rs2070958 T/C (C__64631794_10), and *PDGFA* rs62433334 G/C (C__97285312_10) (Thermo Fisher Scientific, Waltham, MA, USA).

Genotyping quality control included two negative controls in each reaction plate and inspection of amplification curves and allelic discrimination plots. Missing genotype data were rare and occurred only for individual SNPs in single samples. SNP-specific call rates were high, ranging from 98.79% to 100%. The lowest call rate was observed for *TGFB1* rs1800470, for which four genotype calls were missing. Laboratory personnel were blinded to injury status during genotyping, and samples were processed using coded identifiers.

2.4. Statistical Analyses

The statistical analyses were conducted using R software (version 2.0-1, R Foundation for Statistical Computing, <https://cran.r-project.org>, 1 June 2026). In particular, the SNPAssoc package was employed to perform single-locus analysis, encompassing examinations under four genetic models (codominant, dominant, recessive, and overdominant), all based on minor allele frequencies (MAF). Deviations from Hardy–Weinberg equilibrium (HWE) expectations were evaluated for all genotypes and alleles using the chi-square test implemented in R software. Fisher's exact test was used to examine single-allele effects. Haplotype analyses were performed using the haplo.stats package. The haplo.score function was employed to assess the association between allele combinations and injury under different inheritance models (additive, dominant, and recessive), including both magnitude and direction. Additionally, the haplo.group function was utilized to estimate haplotype frequencies. Multifactor dimensionality reduction (MDR) analysis was performed using MDR 3.2.0 software to evaluate potential interactions between polymorphisms located on different chromosomes. The threshold for statistical significance was set at $p < 0.05$ for all analyses, while sex was considered a potential confounding factor. To account for multiple

comparisons across the single-SNP, allele, and haplotype tests, the False Discovery Rate (FDR) was controlled using the Benjamini–Hochberg procedure.

3. Results

The genotype frequencies observed across the entire cohort did not exhibit any notable departure from HWE expectations. The calculated p -values ranged from 0.30 to 0.91. Furthermore, similar observations were noted when the frequencies were evaluated separately in the cases and controls. Both the control and case groups showed genotype frequencies largely consistent with HWE expectations, with p -values ranging from 0.21 to 1.00. The exception was the polymorphism *PDGFA* (rs2070958 T/C), for which expectations were not met across the entire study (p -value = 0.01), and the NCKLR group (p -value = 0.001). Because equilibrium expectations were met in the control group, rs2070958 was retained for subsequent analyses (Table 1).

Table 1. Minor allele frequencies (MAFs) and the probabilities that the genotype frequencies do not differ from Hardy–Weinberg expectations.

	MAF (%)	HWE p -Value All	HWE p -Value NCKLR	HWE p -Value Control
<i>TGFB1</i> (rs1800470 A/G)	allele A (43.81)	0.91	0.54	0.89
<i>TGFB1</i> (rs1800469 A/G)	allele A (38.96)	0.42	0.83	0.21
<i>PDGFA</i> (rs1800814 A/G)	allele A (46.18)	0.66	0.67	1.00
<i>PDGFA</i> (rs2070958 T/C)	allele C (42.20)	0.01	0.001	0.34
<i>PDGFA</i> (rs62433334 G/C)	allele G (31.29)	0.30	1.00	0.21

MAF—minor allele frequency; HWE—Hardy–Weinberg equilibrium; NCKLR—non-contact knee ligament rupture.

No significant associations ($p > 0.05$) were observed for the *TGFB1* (rs1800470 A/G), *TGFB1* (rs1800469 A/G), and *PDGFA* (rs62433334 G/C) polymorphisms for the genotype and allele distributions.

For the *PDGFA* rs2070958 T/C polymorphism, a significant association was observed in the codominant model, with the C/C genotype associated with higher odds of NCKLR compared with T/T homozygotes, although the 95% confidence interval included the null value (OR = 1.77; 95% CI 0.96–3.27; $p = 0.03$). After FDR correction this association did not remain significant ($q = 0.08$). In the genotype-specific comparison, the C/C genotype showed higher odds of NCKLR status compared with the T/T genotype, although the 95% confidence interval included 1.00 (OR = 1.77; 95% CI 0.96–3.27). The recessive model also showed a significant association (T/T–T/C vs. C/C, OR = 2.00; 95% CI 1.16–3.46; $p = 0.01$). This result was borderline significant after FDR correction (OR = 2.00; 95% CI 1.16–3.46; $p = 0.01$, $q = 0.05$). No significant associations were observed at the allele level (Table 2).

For the *PDGFA* (rs1800814 A/G) polymorphism, significant associations were observed under the codominant, dominant, recessive, and allele models. In the codominant model, ORs of 0.57 (95% CI 0.33–0.97) and 0.38 (95% CI 0.19–0.75) were observed for the A/G and A/A genotypes, respectively, relative to the G/G genotype ($p = 0.01$). Significant associations were also observed in the dominant model (G/G vs. A/G–A/A, OR = 0.50; 95% CI 0.31–0.83; $p = 0.01$) and the recessive model (G/G–A/G vs. A/A, OR = 0.53; 95% CI 0.28–0.98; $p = 0.04$). In addition, a significant association was identified at the allele level (A vs. G, OR = 0.60; 95% CI 0.42–0.85; $p = 0.004$). The recessive model showed a weaker association that reached statistical significance and was borderline after FDR correction (G/G–A/G vs. A/A: OR = 0.53; 95% CI: 0.28–0.98; $p = 0.04$, $q = 0.05$). At the allele level, the A allele was associated with lower odds of NCKLR status compared with the G allele (OR = 0.60; 95% CI: 0.42–0.85; $p = 0.004$, $q = 0.02$) (Table 3).

Table 2. Genotype and allele frequency distributions of the *PDGFA* rs2070958 T/C polymorphism in injured and control handball players under different genetic inheritance models.

Model	Genotype	NCKLR	%	Control	%	OR	95% CI	p-Value/q-Value	AIC
codominant	T/T	36	36	85	37.4	1		0.03 */0.08	401.9
	T/C	34	34	102	44.9	0.79	0.45 1.36		
	C/C	30	30	40	17.6	1.77	0.96 3.27		
dominant	T/T	36	36	85	37.4	1		0.80/0.80	406.6
recessive	T/C-C/C	64	64	142	62.6	1.06	0.65 1.74		
	T/T-T/C	70	70	187	82.4	1		0.01 */0.05 #	400.6
overdominant	C/C	30	30	40	17.6	2	1.16 3.46		
	T/T-C/C	66	66	125	55.1	1		0.06 #/0.10	403.2
allele	T/C	34	34	102	44.9	0.63	0.39 1.03		
	T	106	53	272	59.9	1		0.10/0.13	
	C	94	47	182	40.1	1.32	0.93 1.88		

NCKLR—non-contact knee ligament rupture; OR—odds ratio; CI—confidence interval; AIC—Akaike information criterion. * indicates statistical significance ($p < 0.05$ or $q < 0.05$); # indicates borderline significance ($p = 0.05$ – 0.10 or $q = 0.05$ – 0.10).

Table 3. Genotype and allele frequency distributions of the *PDGFA* rs1800814 A/G polymorphism in injured and control handball players according to different inheritance models.

Model	Genotype	NCKLR	%	Control	%	OR	95% CI	p-Value/q-Value	AIC
codominant	G/G	40	40	57	25.1	1		0.01 */0.02 *	400
	A/G	45	45	113	49.8	0.57	0.33 0.97		
	A/A	15	15	57	25.1	0.38	0.19 0.75		
dominant	G/G	40	40	57	25.1	1		0.01 */0.02 *	399.5
recessive	A/G-A/A	60	60	170	74.9	0.5	0.31 0.83		
	G/G-A/G	85	85	170	74.9	1		0.04 */0.05 #	402.3
overdominant	A/A	15	15	57	25.1	0.53	0.28 0.98		
	G/G-A/A	55	55	114	50.2	1		0.43/0.43	406
allele	A/G	45	45	113	49.8	0.83	0.51 1.32		
	G	125	62.5	227	50	1		0.004 */0.02 *	
	A	75	37.5	227	50	0.60	0.42 0.85		

NCKLR—non-contact knee ligament rupture; OR—odds ratio; CI—confidence interval; AIC—Akaike information criterion. * indicates statistical significance ($p < 0.05$ or $q < 0.05$); # indicates borderline significance ($p = 0.05$ – 0.10 or $q = 0.05$ – 0.10).

Haplotype analysis for *PDGFA* (rs1800814 A/G), *PDGFA* (rs2070958 T/C), and *PDGFA* (rs6243334 G/C) was considered only for haplotypes with a frequency of $>5\%$. The most common haplotype was GCC (34%). A significant association was observed for the *PDGFA* A-T-G haplotype, which was less frequent among injured athletes than controls (7% vs. 14%). Significant associations were identified under both the additive (hap-score = -2.45 ; $p = 0.01$), which was borderline after FDR correction ($q = 0.05$). Significant association was also observed in the dominant model (hap-score = -2.20 ; $p = 0.03$), but this did not remain significant after FDR correction ($q = 0.15$) (Figure 1; Table 4).

Potential multi-locus genotype patterns associated with NCKLR status were evaluated using MDR analysis. The multidimensional space of genotype combinations was reduced to a single binary variable representing “high-risk” and “low-risk” categories. This assignment was based on the ratio of NCKLR to controls within each specific genotype combination cell. First, the global threshold was established as the ratio of total cases to total controls in the training dataset. For each multi-locus genotype combination, the local ratio of cases to controls was calculated. If this ratio was greater than or equal to the overall threshold, the specific genotype combination was classified as “high-risk”. Conversely, if the ratio was lower than the overall threshold, the combination was classified as “low-risk”. MDR

analysis identified a significant three-locus model involving *TGFB1* rs1800469, *PDGFA* rs1800814, and *PDGFA* rs2070958 (OR = 2.63; 95% CI 1.40–4.94; $p = 0.002$). Although all five polymorphisms were evaluated, only these three loci were retained in the best-performing MDR model. The genotype combinations assigned to the control group by the MDR model are shown in Table 5. These combinations consistently included the TC or TT genotype at *PDGFA* rs2070958. Model demonstrated maximum cross-validation consistency (CVC = 10/10), indicating high stability across data splits. Furthermore, permutation testing confirmed the statistical significance of this specific multi-locus pattern ($p = 0.013$). However, the testing balanced accuracy (0.60) suggests that, while the interaction is highly significant, its isolated discriminatory performance for NCKLR status remains modest (Table 6).

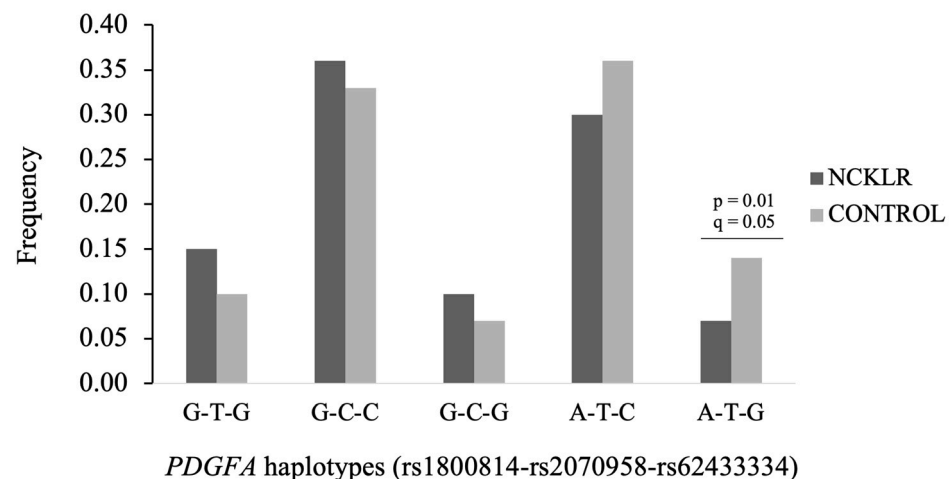


Figure 1. Frequency distributions of *PDGFA* haplotypes defined by rs1800814 A/G, rs2070958 T/C and rs6243334 G/C in the NCKLR ($n = 102$) and control ($n = 229$) groups. The p -value and FDR-adjusted q -value shown for the A-T-G haplotype refer to the additive model.

Table 4. Haplotype frequency distributions and haplotype association analysis for the *PDGFA* rs1800814 A/G, rs2070958 T/C, and rs6243334 G/C polymorphisms in injured and control handball players.

Genotype			Haplotype Frequency			Additive Model		Dominant Model		Recessive Model	
<i>PDGFA</i> rs1800814	<i>PDGFA</i> rs2070958	<i>PDGFA</i> rs6243334	all	NCKLR	Control	Hap-Score	p -Value/ q -Value	Hap-Score	p -Value/ q -Value	Hap-Score	p -Value/ q -Value
G	T	G	0.11	0.15	0.10	1.84	0.07/0.18	1.74	0.08/0.18	1.04	0.30/0.38
G	C	C	0.34	0.36	0.33	1.05	0.29/0.29	0.79	0.43/0.44	1.01	0.31/0.38
G	C	G	0.08	0.10	0.07	1.06	0.29/0.29	0.77	0.44/0.44	NA	NA/NA
A	T	C	0.34	0.30	0.36	−1.57	0.12/0.20	−1.59	0.11/0.18	−0.88	0.38/0.38
A	T	G	0.12	0.07	0.14	−2.45	0.01*/0.05 #	−2.20	0.03*/0.15	−1.79	0.07/0.28

NCKLR—non-contact knee ligament rupture; hap-score—haplotype score statistic. * indicates statistical significance ($p < 0.05$ or $q < 0.05$); # indicates borderline significance ($p = 0.05$ –0.10 or $q = 0.05$ –0.10).

Table 5. Genotype combinations assigned to the low-risk (control group) category by the best MDR model.

<i>TGFB1</i> rs1800470 A/G	<i>TGFB1</i> rs1800469 A/G	<i>PDGFA</i> rs1800814 A/G	<i>PDGFA</i> rs2070958 T/C	<i>PDGFA</i> rs6243334 G/C	Predicted Class	OR (95%CI)	p -Value
-	GG	GG	TC	-	control	2.63	
-	AG	AG	TC	-	control	(1.40–4.94)	0.002 *
-	AA	AA	TT	-	control		

MDR—multifactor dimensionality reduction; “-” indicates polymorphisms not retained in the best MDR model. * indicates statistical significance ($p < 0.05$).

Table 6. Global performance metrics and cross-validation results for the best multifactor dimensionality reduction (MDR) model.

CVC	Train Balanced Accuracy	Testing Balanced Accuracy	Permutation <i>p</i> -Value	Sensitivity
10/10	0.64	0.60	0.01	0.83

4. Discussion

The present study investigated whether genetic variants in *TGFB1* and *PDGFA* are associated with susceptibility to NCKLR among elite handball players. The main finding was that two *PDGFA* polymorphisms, rs2070958 and rs1800814, showed associations with NCKLR status, whereas no significant associations were observed for the *TGFB1* variants investigated. These findings suggest that genetic variability within *PDGFA* may be associated with individual differences in NCKLR status among elite athletes. *PDGFA* encodes platelet-derived growth factor A, which is involved in cell recruitment, proliferation, extracellular matrix remodeling, and tissue repair [33]. Given the importance of these processes for ligament homeostasis and healing, *PDGFA* represents a biologically plausible candidate gene for studies of ligament injury susceptibility. The present results should be interpreted as statistical associations rather than evidence of a direct biological effect on ligament injury susceptibility. Overall, selected *PDGFA* variants were associated with NCKLR status in this cohort of elite handball players. However, because rs2070958 deviated from Hardy–Weinberg equilibrium in the total sample and in the NCKLR group, but not in controls, the associations observed for this variant should be interpreted cautiously and require independent replication. For the *PDGFA* rs2070958 polymorphism, an association with NCKLR status was observed in the codominant model and in the recessive inheritance model. In the codominant model, individuals carrying the C/C genotype had higher odds of NCKLR status than T/T homozygotes (OR = 1.77; 95% CI: 0.96–3.27; $p = 0.03$). However, because the confidence interval included 1.0 and the association did not remain significant after FDR correction ($q = 0.08$), this finding should be interpreted with caution and considered exploratory. In contrast, the recessive model showed a stronger association, with C/C homozygotes exhibiting a twofold higher odds of NCKLR status compared with T-allele carriers (OR = 2.00; 95% CI: 1.16–3.46; $p = 0.01$). After FDR correction, this association remained borderline significant ($q = 0.05$). According to the dbSNP annotation, rs2070958 is located within an intronic region of the *PDGFA* gene [34]. Although intronic variants do not directly affect protein sequence, intronic regions contain regulatory elements that may influence transcriptional activity and alternative splicing [35]. Therefore, the observed association may reflect regulatory mechanisms affecting *PDGFA* activity. No transcriptomic profiling, protein-level analyses, or functional assays were performed; the present study cannot determine whether rs2070958 affects *PDGFA* expression, protein synthesis or downstream signaling activity. Therefore, the functional consequences of this variant remain unknown. To the best of our knowledge, no prior studies have investigated rs2070958 in relation to susceptibility to knee ligament injury. However, Jarosz et al. reported that carriers of the T allele exhibited a more favorable response to platelet-rich plasma therapy in patients with lateral epicondylitis, whereas CC homozygotes demonstrated poorer clinical outcomes and more frequently required additional therapeutic interventions [36]. Although differences in phenotype and study design limit direct comparisons, these findings suggest that rs2070958 may contribute to inter-individual variability in connective tissue healing and remodeling.

A significant association was also observed for the *PDGFA* rs1800814 variant. Similar to rs2070958, rs1800814 is also located within an intronic region of the *PDGFA* gene, suggesting that its effects may be mediated through regulatory rather than protein-coding

mechanisms. In the present study, carriers of the A allele and A-containing genotypes were less frequently represented among injured athletes. The associations remained significant after FDR correction in the codominant, dominant, and allele models, whereas the recessive model was borderline after correction. Notably, the A allele was associated with 40% lower odds of NCKLR status (OR = 0.60; 95% CI: 0.42–0.85; $p = 0.004$) and this association remained significant after FDR correction (OR = 0.60; 95% CI: 0.42–0.85; $p = 0.004$; $q = 0.02$), suggesting a potential protective effect against ligament injury. Although no previous studies have investigated rs1800814 in relation to NCKLR susceptibility, Jarosz et al. reported that carriers of the A allele showed a more favorable response to platelet-rich plasma therapy in patients with lateral epicondylitis. In contrast, GG homozygotes experienced poorer clinical outcomes and more frequently required additional therapeutic interventions [36]. These observations are consistent with the present findings, which demonstrated a protective association of the A allele against NCKLR. The biological mechanisms underlying this association remain unclear. However, *PDGFA* plays an important role in connective tissue regeneration, including fibroblast proliferation, extracellular matrix synthesis, and tissue remodeling, processes essential for ligament maintenance and healing [37,38]. Consequently, genetic variation in *PDGFA* may contribute to inter-individual differences in susceptibility to ligament injury.

In addition to the single-marker associations, haplotype analysis identified a significant association between the *PDGFA* A-T-G haplotype (rs1800814–rs2070958–rs62433334) and NCKLR status. The frequency of the A-T-G haplotype was lower among injured athletes than among controls (7% vs. 14%). Significant associations were observed in both the additive (hap-score = -2.45 ; $p = 0.01$) and dominant (hap-score = -2.20 ; $p = 0.03$) models, whereas the recessive model did not reach statistical significance ($p = 0.07$). After FDR correction, only the additive model remained borderline significant (hap-score = -2.45 ; $p = 0.01$; $q = 0.05$), while the dominant model did not remain significant ($q = 0.15$). Therefore, the haplotype association should be interpreted cautiously and considered exploratory. These findings suggest that combinations of *PDGFA* variants may provide additional information beyond individual SNP analyses. Because haplotypes capture the joint inheritance of neighboring variants, they may better reflect underlying functional variation within the *PDGFA* locus than single polymorphisms alone. Although the biological significance of the A-T-G haplotype remains unclear, the observed association further supports the potential role of *PDGFA* genetic variability in susceptibility to ligament injury. To the best of our knowledge, no previous studies have investigated *PDGFA* haplotypes in relation to the odds of knee ligament rupture, thereby limiting direct comparisons with the existing literature. Although significant p -values indicated associations in the additive and dominant models, these findings were reduced after FDR correction.

MDR analysis further suggested an exploratory statistical multi-locus model involving variants in *PDGFA* and *TGFB1* that was associated with NCKLR status. The best-performing model included *TGFB1* rs1800469, *PDGFA* rs1800814, and *PDGFA* rs2070958 and was significantly associated with injury status (OR = 2.63; 95% CI: 1.40–4.94; $p = 0.002$). Notably, genotype combinations containing T-allele-carrying genotypes (TC and TT) at *PDGFA* rs2070958 were predominantly assigned to the low-risk (control) category by the MDR model. The differential distribution of high-risk and low-risk multi-locus genotype combinations identified by MDR may indicate potential gene–gene interactions between these loci. Similar MDR-derived interaction patterns have previously been interpreted as being consistent with epistatic effects and non-additive genetic interactions between variants [39]. However, MDR was developed primarily as a tool for hypothesis generation and exploratory detection of multi-locus interactions rather than for establishing biological mechanisms [40]. Therefore, the present findings should be interpreted as evidence of

potential statistical interactions rather than direct biological epistasis. Nevertheless, the identified model suggests that the combined effects of multiple genetic variants may contribute to susceptibility to ligament injury beyond the effects of individual polymorphisms. This interpretation is biologically plausible because both TGF- β [41,42] and PDGF [43,44] signaling pathways are involved in connective tissue repair and remodeling, including fibroblast proliferation, extracellular matrix synthesis, and tissue regeneration. Consequently, genetic variation within these pathways may jointly influence tissue adaptation to repetitive mechanical loading and the capacity for ligament healing.

Contrary to our expectations, no significant associations were observed for *TGFB1* polymorphisms rs1800470 and rs1800469. The rs1800470 variant is a functional missense variant [45], whereas rs1800469 is located approximately 2 kb upstream of *TGFB1* within a regulatory region implicated in gene expression control [46]. Given the established role of TGF- β 1 in extracellular matrix remodeling, collagen synthesis, and connective tissue healing [21], these findings suggest that common variation at these loci may have a limited influence on NCKLR status in elite handball players. Notably, Posthumus et al. (2010) also reported no significant association between the *TGFB1* rs1800469 polymorphism and Achilles tendon pathology in Australian and South African cohorts [31]. Although Achilles tendon pathology and knee ligament rupture represent distinct musculoskeletal phenotypes, the concordance of findings across studies may suggest that rs1800469 has a limited effect on susceptibility to connective tissue injury despite its proposed regulatory role in *TGFB1* expression. No association was identified for *PDGFA* rs62433334, an intronic variant for which no functional effects have been clearly established to date. Given the scarcity of available literature and the limited evidence linking this polymorphism to musculoskeletal outcomes, the biological relevance of rs62433334 in ligament injury susceptibility remains unclear.

Although genetic testing cannot currently be used as a standalone tool for injury prediction, identifying genetic variants associated with susceptibility to ligament injury may inform future multifactorial models of injury risk assessment [47–49]. Such models could integrate genetic, biomechanical, physiological, and training-related factors to improve athlete monitoring and support evidence-based injury-prevention strategies in elite sport. Therefore, the present findings should be regarded as preliminary and exploratory, rather than as evidence supporting the current use of genetic testing for individual injury-risk prediction. Predictive panels that include genetic information should be strictly regulated to ensure the protection of athletes' privacy and the privacy of their relatives. Sensitive genetic data should be appropriately coded, and biological samples should be stored securely under the supervision of qualified personnel. Unauthorized disclosure of genetic data could lead to discrimination against athletes by sports clubs, coaches, or insurers on the basis of genetic predispositions related to physical performance or presumed increased injury susceptibility. In addition, the results of such tests should be discussed with a physician or another professional qualified to interpret genetic data in order to reduce the risk of overinterpretation and incorrect conclusions. This type of information may also affect athletes psychologically, potentially leading to deterministic beliefs about their sporting predispositions, which could influence training engagement and athletic performance. Therefore, athletes participating in scientific or commercial genetic testing should be informed about the purpose of the study, the scope of the analyses, and the limitations of genetic test results. Moreover, clubs and coaches should not exert pressure on athletes to participate in such testing, and athletes should have the right to withdraw their consent at any stage [49].

The present study has several limitations. First, although the study included elite handball players competing in the Polish SuperLiga, the cohort was limited to a single

national professional league and comprised only Caucasian athletes, which was defined as one of the inclusion criteria. Given the limited size of the available elite handball cohort, inclusion of athletes from additional ancestral backgrounds would have resulted in small and underpowered subgroups. Moreover, combining participants from different ancestral populations in a single association analysis could introduce population stratification bias, because allele frequencies and genotype–phenotype associations may differ across populations. Therefore, the findings may not be generalizable to athletes from other ethnic backgrounds, competitive levels, or sports disciplines and should be interpreted in relation to Caucasian elite handball players. Future studies should validate these findings in larger cohorts including athletes from diverse populations. Second, the injury group included various non-contact knee ligament ruptures, including ACL, PCL, LCL, MCL, and patellar ligament injuries. Although these injuries share some biomechanical and tissue-remodeling features, they may differ in their specific injury mechanisms and biological determinants, thereby introducing phenotypic heterogeneity. This approach was selected to examine non-contact rupture of major knee ligament structures as a broad sport-related injury phenotype in elite handball players, while maintaining sufficient statistical power for genetic association analyses. The included ligament structures differ in anatomy, biomechanical function, loading profile, injury mechanism, and intrinsic healing capacity. Therefore, combining these injuries may increase statistical power but may also dilute ligament-specific genetic associations. Because the number of non-ACL injuries was limited, subtype-specific analyses were not performed due to the risk of unstable and underpowered estimates. Future studies should validate these findings in larger cohorts and, where possible, focus on anatomically homogeneous outcomes, particularly isolated ACL rupture. Third, the study used a candidate-gene approach and included only selected *TGFB1* and *PDGFA* polymorphisms. These genes were selected because of their biological relevance to cell proliferation, differentiation, extracellular matrix remodeling, and tissue repair processes involved in ligament healing. The analyzed polymorphisms were chosen based on previous literature suggesting their potential clinical relevance or their location within intragenic regions with possible regulatory importance. Nevertheless, this limited SNP panel does not capture the broader genetic architecture of ligament injury susceptibility, which is likely polygenic and influenced by multiple biological pathways. Future studies should include a larger number of variants in genes involved in signaling pathways regulating soft tissue repair. Larger cohorts may also enable genome-wide approaches to identify additional variants associated with soft tissue injury susceptibility and repair. Ligament injury susceptibility is likely polygenic and influenced by many additional genetic and environmental factors. Fourth, detailed environmental and sport-specific exposures, such as cumulative training load, playing position, previous lower limb injuries, neuromuscular control, recovery strategies, and hormonal factors, were not fully evaluated. These variables may modify the relationship between genetic variants and injury susceptibility. Fifth, the *PDGFA* rs2070958 polymorphism deviated from the HWE in the whole cohort and in the NCKLR group, which should be considered when interpreting the observed association. Sixth, haplotype and MDR analyses should be interpreted with caution, as they are exploratory and require validation in larger independent cohorts. Finally, as this was a case–control association study, the findings indicate statistical associations rather than causal relationships. Functional studies are needed to clarify whether the associated *PDGFA* variants influence gene expression, growth factor signaling, connective tissue remodeling, or ligament healing capacity.

5. Conclusions

In conclusion, no significant associations were observed between *TGFB1* polymorphisms rs1800470 and rs1800469 and NCKLR risk, whereas selected *PDGFA* variants were associated with NCKLR status in elite Caucasian handball players. Specifically, carriers of the *PDGFA* rs2070958 C/C genotype exhibited approximately twofold higher odds of injury in the recessive model. Haplotype analysis further indicated that the *PDGFA* A-T-G haplotype was less frequent among injured athletes and was significantly associated with NCKLR status, after FDR correction; only the additive model remained borderline significant, while the dominant association was not retained. Therefore, the haplotype finding should be considered exploratory. In addition, MDR analysis identified a significant three-locus model involving *TGFB1* rs1800469, *PDGFA* rs1800814, and *PDGFA* rs2070958, suggesting potential statistical interactions between *TGFB1* and *PDGFA* variants.

These findings suggest that *PDGFA* genetic variability may contribute to inter-individual differences in susceptibility to non-contact knee ligament rupture. However, given the exploratory nature of the haplotype and MDR analyses, as well as the case-control design, these results require validation in larger and more diverse cohorts. Further studies are needed to determine whether the identified variants are consistently associated with susceptibility to ligament injury across athletic populations and competitive levels. Improved understanding of the genetic factors underlying ligament injury risk may support the development of future multifactorial approaches to injury risk assessment and athlete monitoring.

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Informed Consent Statement: Participants received an information sheet detailing the study’s purpose, procedures, and potential risks and benefits. The study ensured anonymity and confidentiality and obtained written informed consent from all participants prior to inclusion.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACL	anterior cruciate ligament
AIC	Akaike information criterion
CI	confidence interval
HWE	Hardy–Weinberg equilibrium
LCL	lateral collateral ligament
MAF	minor allele frequencies
MCL	medial collateral ligament
MDR	multifactor dimensionality reduction
NCKLR	non-contact knee ligament rupture
OR	odds ratio
PCL	posterior cruciate ligament
PDGF	platelet-derived growth factor
PDGFA	platelet-derived growth factor A gene
PL	patellar ligament
SNP	single-nucleotide polymorphism
TGF- β	transforming growth factor beta
TGFB1	transforming growth factor beta 1 gene

References

1. Milić, V.; Radenković, O.; Čaprić, I.; Mekić, R.; Trajković, N.; Špirtović, O.; Koničanin, A.; Bratić, M.; Mujanović, R.; Preljević, A.; et al. Sports Injuries in Basketball, Handball, and Volleyball Players: Systematic Review. *Life* **2025**, *15*, 529. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Martín-Guzón, I.; Muñoz, A.; Lorenzo-Calvo, J.; Muriarte, D.; Marquina, M.; De La Rubia, A. Injury Prevalence of the Lower Limbs in Handball Players: A Systematic Review. *Int. J. Environ. Res. Public Health* **2021**, *19*, 332. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Aicale, R.; Tarantino, D.; Maffulli, N. Overuse injuries in sport: A comprehensive overview. *J. Orthop. Surg.* **2018**, *13*, 309. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Yang, G.; Rothrauff, B.; Tuan, R. Tendon and ligament regeneration and repair: Clinical relevance and developmental paradigm. *Birth Defects Res. Part C Embryo Today Rev.* **2013**, *99*, 203–222. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Maffulli, N.; Margiotti, K.; Longo, U.G.; Loppini, M.; Fazio, V.M.; Denaro, V. The genetics of sports injuries and athletic performance. *Muscles Ligaments Tendons J.* **2013**, *3*, 173–189. [\[PubMed\]](#)
6. Belozo, F.L.; Belozo, R.S.M.N.; Ricardo Lopes, C.; Yamada, A.K.; Silva, V.R.R. Anterior cruciate ligament: A brief narrative review of main risk factors for injury and re-injury. *J. Bodyw. Mov. Ther.* **2024**, *38*, 92–99. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Compagnin, A.; Della Villa, F. Rehabilitation and Return to Sports of Knee Ligament Injuries. In *Orthopaedic Sports Medicine*; Espregueira-Mendes, J., Karlsson, J., Musahl, V., Ayeni, O.R., Eds.; Springer: Cham, Switzerland, 2025; pp. 1–40. [\[CrossRef\]](#)
8. Belkheili, M.; Cierion, T.; Martineau, P.A. Biomechanical Risk Factors for Increased Anterior Cruciate Ligament Loading and Injury: A Systematic Review. *Orthop. J. Sports Med.* **2025**, *13*, 23259671241312681. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Zebis, M.K.; Aagaard, P.; Andersen, L.L.; Hölmich, P.; Clausen, M.B.; Brandt, M.; Husted, R.S.; Lauridsen, H.B.; Curtis, D.J.; Bencke, J. First-time anterior cruciate ligament injury in adolescent female elite athletes: A prospective cohort study to identify modifiable risk factors. *Knee Surg. Sports Traumatol. Arthrosc.* **2022**, *30*, 1341–1351. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Myklebust, G.; Mæhlum, S.; Holm, I.; Bahr, R. A prospective cohort study of anterior cruciate ligament injuries in elite Norwegian team handball. *Scand. J. Med. Sci. Sports* **1998**, *8*, 149–153. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Krosshaug, T.; Steffen, K.; Kristianslund, E.; Nilstad, A.; Mok, K.-M.; Myklebust, G.; Andersen, T.E.; Holme, I.; Engebretsen, L.; Bahr, R. The Vertical Drop Jump Is a Poor Screening Test for ACL Injuries in Female Elite Soccer and Handball Players: A Prospective Cohort Study of 710 Athletes. *Am. J. Sports Med.* **2016**, *44*, 874–883. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Resch, T.; Krutsch, W.; Weber, J.; Krueckel, J.; Hartz, F.; Alt, V.; Achenbach, L.; Szymiski, D. High incidence of anterior cruciate ligament injuries in professional men's handball: Analysis of the 'ACL registry in German Sports' over seven consecutive seasons. *J. Exp. Orthop.* **2025**, *12*, e70132. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Chia, L.; De Oliveira Silva, D.; Whalan, M.; McKay, M.J.; Sullivan, J.; Fuller, C.W.; Pappas, E. Non-contact Anterior Cruciate Ligament Injury Epidemiology in Team-Ball Sports: A Systematic Review with Meta-analysis by Sex, Age, Sport, Participation Level, and Exposure Type. *Sports Med.* **2022**, *52*, 2447–2467. [\[CrossRef\]](#) [\[PubMed\]](#)

14. Sümegi, T.; Sonkodi, B.; Havanecz, K.; Berkes, I.; Kopper, B. Biomechanical Model of Non-Contact Anterior Cruciate Ligament Injury Concerning Shin Angle and Field Surface Traction Parameters—With a Piezo2 Interpretation. *Sports* **2025**, *13*, 414. [CrossRef] [PubMed]
15. September, A.; Schwellnus, M.; Collins, M. Tendon and ligament injuries: The genetic component. *Br. J. Sports Med.* **2007**, *41*, 241–246. [CrossRef] [PubMed]
16. Ribbans, W.J.; September, A.V.; Collins, M. Tendon and Ligament Genetics: How Do They Contribute to Disease and Injury? A Narrative Review. *Life* **2022**, *12*, 663. [CrossRef] [PubMed]
17. Leońska-Duniec, A. Genetic Susceptibility to Sport-Related Muscle Injuries: Insights from the Literature and Novel Gene Candidates. *Int. J. Mol. Sci.* **2025**, *26*, 11175. [CrossRef] [PubMed]
18. Collins, M.; September, A.V.; Posthumus, M. Biological variation in musculoskeletal injuries: Current knowledge, future research and practical implications. *Br. J. Sports Med.* **2015**, *49*, 1497–1503. [CrossRef] [PubMed]
19. Lim, T.; Santiago, C.; Pareja-Galeano, H.; Iturriaga, T.; Sosa-Pedreschi, A.; Fuku, N.; Pérez-Ruiz, M.; Yvert, T. Genetic variations associated with non-contact muscle injuries in sport: A systematic review. *Scand. J. Med. Sci. Sports* **2021**, *31*, 2014–2032. [CrossRef] [PubMed]
20. Rahim, M.; Collins, M.; September, A. Genes and Musculoskeletal Soft-Tissue Injuries. In *Medicine and Sport Science*; Posthumus, M., Collins, M., Eds.; S. Karger AG: Basel, Switzerland, 2016; Volume 61, pp. 68–91. [CrossRef] [PubMed]
21. Molloy, T.; Wang, Y.; Murrell, G.A.C. The Roles of Growth Factors in Tendon and Ligament Healing. *Sports Med.* **2003**, *33*, 381–394. [CrossRef] [PubMed]
22. Thomopoulos, S.; Parks, W.C.; Rifkin, D.B.; Derwin, K.A. Mechanisms of tendon injury and repair. *J. Orthop. Res.* **2015**, *33*, 832–839. [CrossRef] [PubMed]
23. Pryce, B.A.; Watson, S.S.; Murchison, N.D.; Staverosky, J.A.; Dünker, N.; Schweitzer, R. Recruitment and maintenance of tendon progenitors by TGF β signaling are essential for tendon formation. *Development* **2009**, *136*, 1351–1361. [CrossRef] [PubMed]
24. Younan, S.A.; Ueland, T.E.; Savitz, B.L.; Jerome, R.N.; Budine, T.D.; Hawkins, A.T.; Thayer, W.P.; Wu, D.T.; Lynch, S.E.; Clark, C.R. Recombinant Platelet-Derived Growth Factor in Tissue Repair: A Review Exploring Frontiers in Regenerative Medicine. *Plast. Reconstr. Surg.* **2026**, *157*, 759–770. [CrossRef] [PubMed]
25. Li, Y.; Liu, X.; Liu, X.; Peng, Y.; Zhu, B.; Guo, S.; Wang, C.; Wang, D.; Li, S. Transforming growth factor- β signalling pathway in tendon healing. *Growth Factors* **2022**, *40*, 98–107. [CrossRef] [PubMed]
26. Kim, K.K.; Sheppard, D.; Chapman, H.A. TGF- β 1 Signaling and Tissue Fibrosis. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*, a022293. [CrossRef] [PubMed]
27. Anusaksathien, O.; Webb, S.A.; Jin, Q.-M.; Giannobile, W.V. Platelet-Derived Growth Factor Gene Delivery Stimulates ex Vivo Gingival Repair. *Tissue Eng.* **2003**, *9*, 745–756. [CrossRef] [PubMed]
28. Zhao, T.; Zhao, W.; Chen, Y.; Li, V.S.; Meng, W.; Sun, Y. Platelet-derived growth factor-D promotes fibrogenesis of cardiac fibroblasts. *Am. J. Physiol.-Heart Circ. Physiol.* **2013**, *304*, H1719–H1726. [CrossRef] [PubMed]
29. Martelossi Cebinelli, G.C.; Paiva Trugilo, K.; Badaró Garcia, S.; Brajão De Oliveira, K. TGF- β 1 functional polymorphisms: A review. *Eur. Cytokine Netw.* **2016**, *27*, 81–89. [CrossRef] [PubMed]
30. Cohen, C.; Leal, M.F.; Loyola, L.C.; Santos, S.E.B.; Ribeiro-dos-Santos, Â.K.C.; Belangero, P.S.; Figueiredo, E.A.; Wajnsztein, A.; De Oliveira, A.M.; Smith, M.C.; et al. Genetic variants involved in extracellular matrix homeostasis play a role in the susceptibility to frozen shoulder: A case-control study. *J. Orthop. Res.* **2019**, *37*, 948–956. [CrossRef] [PubMed]
31. Posthumus, M.; Collins, M.; Cook, J.; Handley, C.J.; Ribbans, W.J.; Smith, R.K.W.; Schwellnus, M.P.; Raleigh, S.M. Components of the transforming growth factor- family and the pathogenesis of human Achilles tendon pathology--A genetic association study. *Rheumatology* **2010**, *49*, 2090–2097. [CrossRef] [PubMed]
32. Morris, R.W.; Kaplan, N.L. On the advantage of haplotype analysis in the presence of multiple disease susceptibility alleles. *Genet. Epidemiol.* **2002**, *23*, 221–233. [CrossRef] [PubMed]
33. Zhao, Q.; Che, F.; Liu, W.; Hou, C.; Yu, L.; Hou, Y.; Xu, L. PDGF signaling in cartilage regeneration: Molecular mechanisms and cellular effects. *Front. Cell Dev. Biol.* **2026**, *14*, 1778703. [CrossRef] [PubMed]
34. National Center for Biotechnology Information. (n.d.). rs2070958 RefSNP Report—dbSNP—NCBI [Database Record]. National Library of Medicine (US), National Center for Biotechnology Information. dbSNP. Available online: <https://www.ncbi.nlm.nih.gov/snp/rs2070958> (accessed on 10 June 2026).
35. Rigau, M.; Juan, D.; Valencia, A.; Rico, D. Intronic CNVs and gene expression variation in human populations. *PLoS Genet.* **2019**, *15*, e1007902. [CrossRef] [PubMed]
36. Jarosz, A.; Szyluk, K.; Iwanicka, J.; Balcerzyk, A.; Nowak, T.; Iwanicki, T.; Negru, M.; Kalita, M.; Francuz, T.; Garczorz, W.; et al. What Role Does PDGFA Gene Polymorphisms Play in Treating Tennis Elbow with PRP? A Prospective Cohort Study. *J. Clin. Med.* **2022**, *11*, 3504. [CrossRef] [PubMed]
37. Chen, Y.; Jiang, L.; Lyu, K.; Lu, J.; Long, L.; Wang, X.; Liu, T.; Li, S. A Promising Candidate in Tendon Healing Events—PDGF-BB. *Biomolecules* **2022**, *12*, 1518. [CrossRef] [PubMed]

38. Wang, Y.; Li, J. Current progress in growth factors and extracellular vesicles in tendon healing. *Int. Wound J.* **2023**, *20*, 3871–3883. [[CrossRef](#)] [[PubMed](#)]
39. Xu, H.-M.; Sun, X.-W.; Qi, T.; Lin, W.-Y.; Liu, N.; Lou, X.-Y. Multivariate Dimensionality Reduction Approaches to Identify Gene-Gene and Gene-Environment Interactions Underlying Multiple Complex Traits. *PLoS ONE* **2014**, *9*, e108103. [[CrossRef](#)] [[PubMed](#)]
40. Motsinger, A.A.; Ritchie, M.D. Multifactor dimensionality reduction: An analysis strategy for modelling and detecting gene—gene interactions in human genetics and pharmacogenomics studies. *Hum. Genom.* **2006**, *2*, 318. [[CrossRef](#)] [[PubMed](#)]
41. Massagué, J.; Sheppard, D. TGF- β signaling in health and disease. *Cell* **2023**, *186*, 4007–4037. [[CrossRef](#)] [[PubMed](#)]
42. Ren, M.; Yao, S.; Chen, T.; Luo, H.; Tao, X.; Jiang, H.; Yang, X.; Zhang, H.; Yu, S.; Wang, Y.; et al. Connective Tissue Growth Factor: Regulation, Diseases, and Drug Discovery. *Int. J. Mol. Sci.* **2024**, *25*, 4692. [[CrossRef](#)] [[PubMed](#)]
43. Irma, J.; Kartasasmita, A.S.; Kartiwa, A.; Irfani, I.; Rizki, S.A.; Onasis, S. From Growth Factors to Structure: PDGF and TGF- β in Granulation Tissue Formation. A Literature Review. *J. Cell. Mol. Med.* **2025**, *29*, e70374. [[CrossRef](#)] [[PubMed](#)]
44. Evrova, O.; Buschmann, J. In vitro and in vivo effects of PDGF-BB delivery strategies on tendon healing: A review. *Eur. Cell. Mater.* **2017**, *34*, 15–39. [[CrossRef](#)] [[PubMed](#)]
45. National Center for Biotechnology Information. (n.d.). rs1800470 RefSNP Report—dbSNP—NCBI [Database Record]. National Library of Medicine (US), National Center for Biotechnology Information. dbSNP. Available online: <https://www.ncbi.nlm.nih.gov/snp/rs1800470> (accessed on 10 June 2026).
46. National Center for Biotechnology Information. (n.d.). rs1800469 RefSNP Report—dbSNP—NCBI [Database Record]. National Library of Medicine (US), National Center for Biotechnology Information. dbSNP. Available online: <https://www.ncbi.nlm.nih.gov/snp/rs1800469> (accessed on 10 June 2026).
47. Williams, A.G.; Wackerhage, H.; Day, S.H. Genetic Testing for Sports Performance, Responses to Training and Injury Risk: Practical and Ethical Considerations. In *Medicine and Sport Science*; Posthumus, M., Collins, M., Eds.; S. Karger AG: Basel, Switzerland, 2016; Volume 61, pp. 105–119. [[CrossRef](#)] [[PubMed](#)]
48. Vlahovich, N.; Fricker, P.A.; Brown, M.A.; Hughes, D. Ethics of genetic testing and research in sport: A position statement from the Australian Institute of Sport. *Br. J. Sports Med.* **2017**, *51*, 5–11. [[CrossRef](#)] [[PubMed](#)]
49. Bojarczuk, A. Ethical Aspects of Human Genome Research in Sports—A Narrative Review. *Genes* **2024**, *15*, 1216. [[CrossRef](#)] [[PubMed](#)]

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