Journal of
Personalized Medicine

MDPI

Review

Translational Genetics in Precision Rehabilitation: A Scoping Review of Genomic Variability for Personalized Musculoskeletal and Regenerative Outcomes

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Abstract

Background: Genetic variation may contribute to differences in musculoskeletal phenotypes and recovery, but its value for selecting rehabilitation treatments remains uncertain. This scoping review maps evidence linking genetic variants to musculoskeletal traits, exercise adaptation, pain, and outcomes following regenerative interventions. **Methods:** PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for English-language studies published from January 2000 through October 2026. Reporting followed PRISMA-ScR. Human genetic association and intervention studies were charted and synthesized narratively. Mechanistic findings were considered separately from clinical evidence. Sample sizes and quantitative results were summarized where available, distinguishing genotype–phenotype associations, genotype-associated changes over time, and genotype-by-treatment interactions. **Results:** Studies examined variants in genes related to muscle function, extracellular-matrix organization, growth-factor signaling, inflammation, and pain processing. Findings varied by population, sex, outcome, and intervention. In a resistance-training cohort of 602 adults, ACTN3 genotype explained approximately 2% of strength-gain variation, with an association observed in women but not men. Six platelet-rich plasma reports arose from one cohort of 107 patients and 132 elbows, limiting independent replication. Most findings represented phenotype or outcome associations rather than evidence that genotype modifies treatment benefit relative to a comparator. **Conclusions:** Current evidence supports further investigation of genetic contributions to rehabilitation-related variability but does not justify routine genotyping to select interventions or prescribe loading, intensity, or recovery intervals. Clinical translation requires independent replication, appropriately controlled genotype-by-treatment analyses, and prospective demonstration of benefit beyond established clinical assessment.

Keywords: musculoskeletal disorders; single-nucleotide polymorphisms (SNPs); rehabilitation; precision medicine; genetic polymorphisms

Academic Editor: Liang Cheng

Received: 2 September 2026
Revised: 24 October 2026
Accepted: 29 October 2026
Published: 31 October 2026

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1. Introduction

Musculoskeletal disorders represent one of the leading causes of disability and chronic pain worldwide, with a steadily increasing prevalence driven by population aging and lifestyle-related risk factors. These conditions may arise from hereditary, congenital, or acquired pathological processes, including infectious, inflammatory, degenerative, traumatic, cancer or developmental origins [1]. Chemotherapy has also been shown to cause musculoskeletal pain or stiffness in breast cancer patients [2]. Given their multifactorial nature, effective management requires an integrated and multidisciplinary approach combining pharmacological treatments, minimally invasive procedures, and a broad spectrum of non-invasive rehabilitation strategies [3]. Musculoskeletal rehabilitation aims to restore functional capacity, optimize physical performance, and alleviate pain in individuals with impairments affecting muscles, bones, joints, and connective tissues. Rehabilitation programs typically incorporate therapeutic exercise, manual therapy, neuromuscular re-education, and adjunctive modalities delivered by interdisciplinary teams [4].

Over the past decade, advancements in rehabilitation science have improved therapeutic possibilities. However, a persistent and clinically significant challenge remains: substantial inter-individual variability in rehabilitation outcomes [5]. Patients receiving similar evidence-based rehabilitation protocols often demonstrate markedly different improvements in muscle strength, pain reduction, and functional recovery. This heterogeneity suggests that conventional "one-size-fits-all" approaches may fail to account for underlying biological determinants that shape adaptive responses to rehabilitation interventions [6,7]. Consequently, there is growing recognition of the need for precision rehabilitation, an emerging paradigm that seeks to tailor therapeutic strategies according to individual biological, functional, and clinical characteristics.

Among the biological contributors to inter-individual variability, genetic polymorphisms have emerged as a potentially critical yet under-integrated factor in rehabilitation research. Gene polymorphism refers to the coexistence of two or more relatively common alleles within a population, each present in at least 1% of individuals [8]. These naturally occurring DNA variations contribute to differences in physiological traits, disease susceptibility, and responses to both pharmacological and non-pharmacological treatments. Although inherited diseases account for only approximately 0.1% of genomic variation, the majority of human genetic diversity results from single-nucleotide polymorphisms (SNPs) [9–11]. Genetic influences on musculoskeletal biology are substantial; it has been estimated that genetic variation explains more than 50% of the variability in muscle mass, muscle strength, and physical performance [12,13]. Nevertheless, the specific polymorphisms that modulate muscle adaptation, injury susceptibility, and responsiveness to rehabilitation interventions remain incompletely characterized [8]. Understanding these genetic influences may provide a mechanistic basis for predicting therapeutic responsiveness and optimizing individualized rehabilitation programs.

Therefore, the primary objective of this scoping review is to systematically delineate the impact of single-nucleotide polymorphisms on inter-individual responsiveness to musculoskeletal rehabilitation interventions. By characterizing the specific genetic variants associated with functional recovery, muscular adaptations, and pain alleviation, this paper seeks to establish a mechanistic framework bridging musculoskeletal genomics with clinical practice, ultimately advancing the realization of tailored, patient-specific rehabilitation protocols.

2. Methods

2.1. Scoping Review Strategy

To ensure a systematic and transparent scoping review process, we adopted the methodological framework proposed by Arksey and O'Malley (2005), further refined by the Joanna Briggs Institute (JBI) for scoping reviews, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [14]. The protocol focused on identifying, categorizing, and mapping the translational evidence linking candidate gene variants to musculoskeletal tissue healing, mechanobiological adaptation, and precision rehabilitation outcomes. A formal a priori review protocol was not prospectively registered in public registries (e.g., PROSPERO or Open Science Framework); however, all methodological stages, eligibility criteria, and analytic pathways were predefined and strictly followed throughout the review process.

2.2. Literature Search Strategy

A systematic, multi-database literature search was designed and executed across four major electronic databases and academic platforms: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, covering records published between January 2000 and October 2026. The comprehensive search architecture integrated controlled vocabularies with targeted title/abstract/keyword free-text terms. The search syntax was organized into three core Boolean logic blocks (Supplementary Table S2):

(a) Target Musculoskeletal Pathology and Tissue Domain: (e.g., "musculoskeletal diseases", "tendinopathy", "rotator cuff", "anterior cruciate ligament", "muscle injury", "cartilage", "osteoarthritis", "muscle strength", "muscle function").
(b) Genetic Polymorphism Domain: (e.g., "polymorphism, single nucleotide", "SNP", "SNPs", "genotype", "genetic variant*", "genetic polymorphism*", "gene variant*").
(c) Intervention and Functional Recovery Domain: (e.g., "rehabilitation", "physiotherapy", "physical therapy", "exercise therapy", "resistance training", "functional recovery", "tissue healing", "platelet-rich plasma", "photobiomodulation", "low-intensity pulsed ultrasound").

Language was restricted to English-language publications. Reference lists of pertinent reviews and selected primary articles were hand-searched to ensure complete coverage.

The initial database searches were conducted between 1 and 31 August 2026, and an updated search was performed on 1 October 2026 to identify additional eligible records published or indexed since the initial search.

2.3. Eligibility Criteria (Inclusion and Exclusion)

Eligibility criteria were established a priori using the Population, Concept, and Context (PCC) framework recommended by the Joanna Briggs Institute (JBI).

Population: Human participants of any age or athletic background studied in relation to musculoskeletal function, injury susceptibility, tissue pathology, recovery, or clinical outcomes relevant to rehabilitation. Eligible populations included individuals undergoing rehabilitation or treatment, participants evaluated following musculoskeletal injury, athletes assessed for injury susceptibility, and healthy or community-dwelling populations assessed for relevant musculoskeletal phenotypes, such as muscle strength, muscle mass, muscle hypertrophy, tendon or ligament pathology, and sarcopenia-related traits.

Concept: Studies investigating candidate genetic variations, including single-nucleotide polymorphisms (SNPs), repeat polymorphisms, or other targeted genotypes,

in relation to at least one of the following: (1) musculoskeletal structural or functional phenotypes; (2) susceptibility to musculoskeletal injury or pathology; (3) adaptation to exercise or mechanical loading; (4) tissue healing or recovery; or (5) clinical, functional, or patient-reported outcomes following rehabilitation or regenerative interventions. These evidence categories were distinguished during synthesis because baseline genotype–phenotype associations and injury-susceptibility findings do not, by themselves, demonstrate differential treatment response.

Context: Musculoskeletal rehabilitation, structured exercise or resistance training, mechanical loading, physical therapy, biophysical modalities, and regenerative interventions such as platelet-rich plasma (PRP). Observational studies without an intervention were eligible when they investigated a prespecified musculoskeletal phenotype or injury-related outcome relevant to the review. Studies reporting genetic associations with circulating biomarkers alone, without a directly relevant musculoskeletal phenotype or clinical outcome, were treated as contextual background rather than eligible primary studies.

2.4. Exclusion Criteria

Records were excluded if they met any of the following predefined conditions:

1. Absence of candidate genetic profiling or genotypic stratification.
2. Focus on non-musculoskeletal pathologies without functional musculoskeletal or peripheral soft-tissue involvement.
3. Lack of any eligible musculoskeletal structural or functional phenotype, injury-susceptibility outcome, exercise or mechanical-loading response, tissue-healing or recovery endpoint, or clinical outcome relevant to rehabilitation. Studies reporting only genetic associations with circulating biomarkers, without a directly relevant musculoskeletal phenotype or clinical outcome, were not included in the primary evidence set.
4. Purely in vitro or preclinical animal designs without clinical correlation or phenotypic validation.
5. Ineligible publication types: conference abstracts lacking verifiable methodology/full text, editorials, commentaries, and narrative reviews providing no primary data.

Electronic search limits and pre-specified filters were applied where available to restrict results to peer-reviewed, English-language, original human research articles published from January 2000 to October 2026. Conference abstracts, proceedings without full published methodological reports, book chapters, non-peer-reviewed preprints, and editorial commentaries were systematically filtered out during the search execution and initial screening. This exclusion was instituted because preliminary abstracts and book chapters inherently lack complete primary genotyping methodologies, transparent allelic frequency distributions, and detailed mechanobiological rehabilitation protocols necessary for rigorous methodological evaluation and narrative synthesis.

2.5. Study Selection and Data Extraction

Literature management and duplicate identification were executed using standard reference management platforms. Following automated and manual deduplication, titles and abstracts were independently screened by two reviewers against the predefined eligibility criteria. Full-text articles of potentially relevant citations were retrieved and subjected to comprehensive evaluation. Disagreements regarding inclusion were resolved through structured consensus or adjudication by a third senior investigator.

Data from the finalized included studies were extracted using a standardized, piloted charting form. Extracted parameters comprised:

- Study identification (first author, publication year, country/geographic setting);
- Target gene, specific polymorphism/SNP (rs identification number), and evaluated alleles;
- Study design and cohort characteristics (sample size, participant demographics, baseline athletic/clinical status);
- Rehabilitation, mechanical loading, or orthobiologic intervention parameters (modality, duration, frequency, follow-up window);
- Primary clinical, functional, and structural outcomes (e.g., peak power, 1RM strength, muscle cross-sectional area, PROM scores [VAS, PRTEE, QuickDASH], pain persistence, and biological markers);

Level of Evidence (LoE) assigned in accordance with the Oxford Centre for Evidence-Based Medicine (OCEBM) criteria.

2.6. Study Selection Flow and Search Yield

The search across PubMed (n = 119), Scopus (n = 443), Web of Science (n = 1586), and Google Scholar (n = 819) retrieved a total of 2967 records. Following the removal of 1051 duplicates, 1916 titles and abstracts were screened, leading to the exclusion of 1828 records. The remaining 88 full-text reports were assessed for detailed eligibility, of which 70 reports were excluded with clear justification.

A final set of 18 independent primary cohorts met all eligibility criteria (represented across 21 published reports; noting that six reports [15–20] originate from a single shared prospective PRP lateral epicondylitis registry comprising 107 patients and 132 elbows) (Supplementary Table S1). The complete selection pathway is illustrated in the PRISMA 2020 Flow Diagram (Figure 1).

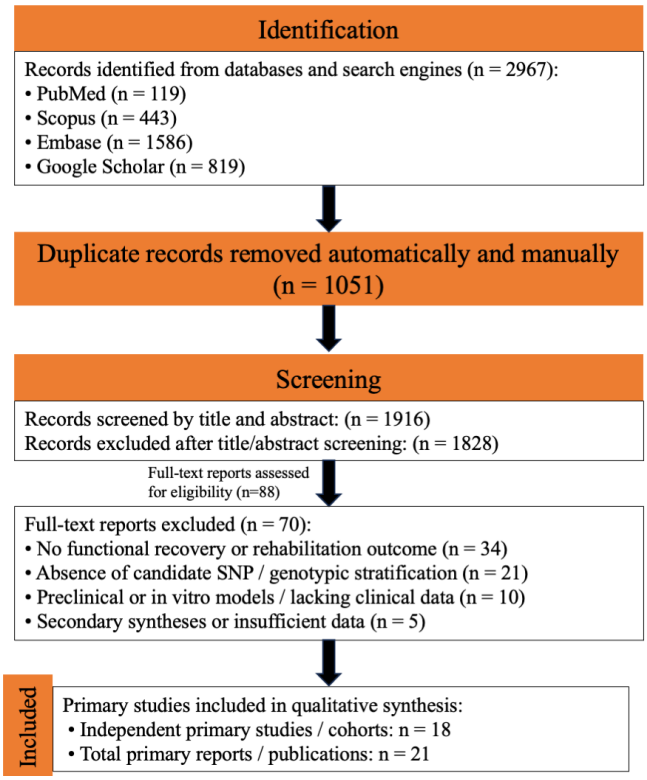


Figure 1. PRISMA flowchart. Note: Six reports derive from a single shared prospective PRP tennis elbow cohort (107 patients, 132 elbows).

2.7. Evidence Synthesis and Translational Framework Development

Given the substantial heterogeneity in patient populations, genetic markers, rehabilitation protocols, and outcome measures across the included literature, quantitative meta-analysis was neither feasible nor methodologically appropriate. Therefore, a structured qualitative and narrative synthesis was performed.

Included genetic variants were synthesized into primary functional axes reflecting their core biological pathways:

1. Myogenesis and Structural Remodeling: (e.g., ACTN3, MSTN, ACVR2B, COL1A1, COL5A1).
2. Vascularization and Tissue Angiogenesis: (e.g., VEGFA, PDGFA, PDGFB, PDGFRA, PDGFRB).
3. Metabolic, Endocrine, and Neurotrophic Adaptation: (e.g., IGF1, CNTF, VDR, ESR1).
4. Inflammation Resolution and Nociceptive Neuroplasticity: (e.g., IL6, COMT, BDNF, OPRM1).

These synthesized primary cohorts directly informed the translational evidence matrices, providing the biological rationale for constructing patient-tailored mechanobiological decision trees in precision musculoskeletal rehabilitation.

For studies reporting quantitative genetic associations or intervention-related outcomes, we extracted sample sizes, genetic comparisons, outcome measures, effect estimates, 95% confidence intervals, and *p*-values where available. We also classified the analytical approach to distinguish formal genotype-by-intervention interactions from genotype-associated changes over time, baseline genotype–phenotype associations, and other exploratory analyses. The quantitative findings and analysis classifications are summarized in Supplementary Table S3. Statistics not reported in the original publications were recorded as unavailable when they could not be reliably derived from the reported data.

2.8. Use of AI-Assisted Language Tools

During the preparation of this manuscript, AI-assisted language models (OpenAI ChatGPT-6) and grammar editing software Chrome Extension 14.1342.0 (Grammarly) were utilized solely to optimize English language fluency, grammatical structure, and stylistic readability. No AI software was employed to conduct literature searches, execute study screening or selection, perform data extraction, assess methodological quality, generate scientific figures, or formulate clinical interpretations and conclusions. All final text, figures, tables, and mechanistic hypotheses were conceptualized, critically reviewed, verified, and approved by the authors, who assume full responsibility for the integrity and accuracy of the manuscript.

3. Molecular Basis of Musculoskeletal Regeneration

3.1. Skeletal Muscle Regeneration

Skeletal muscle repair relies primarily on satellite cells, a specialized population of quiescent muscle stem cells that become activated following injury and in response to inflammatory signals, including tumor necrosis factor (TNF)-α and interferon-gamma (IFN-γ) [21]. Once activated, satellite cells proliferate, differentiate, and fuse to form or repair myofibers [22]. Myogenic transcription factors, including MyoD, myogenin, and paired box protein 7 (Pax7), regulate this process. Pax7 is essential for satellite-cell maintenance and self-renewal, helping preserve the stem-cell pool required for muscle regeneration [23]. Insulin-like growth factor 1 (IGF-1) also contributes to muscle recovery by supporting anabolic signaling and satellite-cell activity. Its effects include activation of the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR)

pathway, which promotes protein synthesis and muscle growth [24]. Exercise provides an important stimulus for muscle adaptation, with aerobic and resistance exercise influencing anabolic and atrophy-related signaling pathways [25]. Mechanical forces are sensed by cellular mechanotransduction systems, including integrins and the mechanosensitive ion channel Piezo1. These systems can engage downstream signaling pathways involving focal adhesion kinase (FAK) and Yes-associated protein (YAP), linking mechanical loading to cellular responses [26,27]. Although these mechanisms provide a biological basis for studying variation in responses to exercise and loading, their presence alone does not establish that a specific genetic variant predicts an individual's rehabilitation response.

3.2. Inflammatory and Immune Signaling

Inflammatory and immune signals help coordinate skeletal muscle repair by regulating satellite-cell activity and the transition from tissue damage to regeneration. Exercise-associated cytokines, including interleukin-6 (IL-6), interleukin-7 (IL-7), and interleukin-15 (IL-15), have been implicated in the regulation of muscle-cell proliferation, differentiation, and maintenance [28]. Anti-inflammatory cytokines such as interleukin-10 (IL-10) can also contribute to the resolution of inflammation and the establishment of a tissue environment that supports repair [21]. These effects depend on the cytokine involved, its concentration, the timing of expression, and the physiological or pathological context.

The inflammatory response is therefore neither uniformly beneficial nor uniformly detrimental: appropriately timed signaling supports regeneration, whereas excessive or prolonged inflammation may interfere with tissue recovery. These mechanisms provide a rationale for investigating whether genetic variation in inflammatory pathways is associated with differences in muscle-related phenotypes or responses to exercise. However, associations with cytokine levels or muscle-damage markers do not, by themselves, demonstrate that genotype can determine rehabilitation intensity, session frequency, or recovery intervals.

3.3. microRNAs and Regenerative Regulation

Muscle-specific microRNAs (miRNAs), collectively known as myomiRs, contribute to the regulation of skeletal muscle development, adaptation, and regeneration. Important myomiRs include miR-1, miR-133a/b, and miR-206, which regulate gene-expression networks involved in myogenic differentiation and muscle repair [29,30]. miR-206 has been implicated in the regulation of satellite-cell differentiation, including through interactions with Pax7-associated regulatory networks [31]. It has also been linked to brain-derived neurotrophic factor (BDNF)-related signaling at the neuromuscular junction, suggesting a potential role in the maintenance of muscle innervation and function [32].

Experimental studies have further investigated the effects of miR-1 and miR-133 administration on muscle regeneration in animal models, although these findings do not establish their therapeutic efficacy in humans [31].

Together, these findings indicate that myomiRs participate in molecular processes relevant to muscle regeneration. However, evidence of their involvement in tissue repair does not establish that naturally occurring genetic variants affecting miRNA expression or activity predict individual rehabilitation outcomes. Whether variation in miRNA-related pathways contributes to clinically meaningful differences in recovery following exercise or rehabilitation interventions remains to be determined.

3.4. BMP Signaling Pathways in Bone Repair

Recent advances in molecular biology have elucidated several signaling pathways that regulate bone formation and repair. Among these, bone morphogenetic proteins (BMPs), members of the transforming growth factor-β (TGF-β) superfamily, play a central role in both skeletal development and fracture healing. BMPs initiate signaling cascades that drive the differentiation of mesenchymal stem cells (MSCs) into osteoblasts, the primary bone-forming cells [33].

BMP signaling occurs predominantly through canonical SMAD-dependent pathways, in which BMP ligands bind to heterotetrameric receptor complexes composed of type I receptors (BMPR1A, BMPR1B, and ACVR1) and type II receptors. This interaction induces phosphorylation of receptor-regulated SMAD proteins (SMAD1, SMAD5, and SMAD8), which subsequently form complexes with SMAD4 and translocate to the nucleus to regulate transcription of osteogenic genes. In parallel, non-canonical SMAD-independent pathways involving mitogen-activated protein kinases (MAPKs) such as ERK and p38, as well as PI3K/AKT signaling, also contribute to osteoblast proliferation, differentiation, and survival. Disruptions in BMP signaling impair bone healing and remodeling, underscoring its critical role in maintaining skeletal integrity [34–36].

Beyond osteoblast differentiation, BMPs also participate in the regulation of osteoclastogenesis and bone resorption, highlighting their dual role in skeletal remodeling [37]. Osteoclasts, which originate from monocyte/macrophage lineages, resorb damaged bone and release coupling factors such as Wnt1, GJA1, and SPHK1 that recruit osteoblast precursors to resorption sites. BMP signaling within osteoclasts, particularly through BMPR1A, modulates osteoblast–osteoclast coupling and helps coordinate bone turnover [38]. Experimental deletion of BMPR1A in osteoclasts in mice has been shown to enhance osteoblastic bone formation, suggesting that BMP signaling may restrain excessive bone formation to preserve skeletal homeostasis [39]. In addition, bone remodeling is tightly regulated by the receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) signaling axis, which controls osteoclast differentiation and activity and interacts with both BMP and Wnt pathways [40]. Clinically, recombinant human BMPs (rhBMP-2 and rhBMP-7) have been employed to stimulate bone regeneration in specific orthopedic settings [41]. However, these agents may paradoxically enhance osteoclastic activity and bone resorption, emphasizing the need for careful therapeutic modulation of BMP-related pathways. Collectively, these findings establish BMP signaling as an important regulator of skeletal development and remodeling. Although BMP-based approaches have been investigated for bone regeneration in selected orthopedic settings, their effects on tissue repair should be distinguished from evidence of improved functional recovery or differential responsiveness to rehabilitation.

3.5. Wnt/β-Catenin Signaling and Osteogenic Regulation

In addition to BMP signaling, the Wnt/β-catenin pathway represents another central regulatory mechanism governing osteogenic differentiation and skeletal remodeling [42]. Activation of Wnt signaling stabilizes β-catenin, allowing its accumulation in the cytoplasm and subsequent translocation to the nucleus, where it regulates transcription of osteogenic genes (Figure 2B). This process is initiated when Wnt ligands bind to Frizzled receptors and the co-receptors low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6), leading to inhibition of the β-catenin destruction complex [42]. Dysregulation of this signaling axis, including alterations in endogenous inhibitors such as sclerostin or Dickkopf-1 (DKK1), can significantly affect bone mass and fracture susceptibility [42]. Mutations or functional disturbances within Wnt pathway components have been associated with skeletal deformities, reduced bone density, and impaired bone

repair. The Wnt pathway also interacts extensively with BMP signaling and osteoclast-derived coupling factors, forming an integrated regulatory network that finely tunes skeletal remodeling dynamics [37]. Within this regulatory network, RUNX2 (Runt-related transcription factor 2) functions as a key transcriptional regulator of osteoblast differentiation and is widely recognized as a master regulator of skeletogenesis. RUNX2 is essential for the differentiation of pluripotent mesenchymal cells into osteoblasts and contributes to the maintenance of bone matrix protein gene expression in mature osteoblasts [43].

Bone repair involves a tightly coordinated sequence of cellular and molecular events, including the release of growth factors embedded within the bone matrix during osteoclastic resorption. These factors recruit osteoblast precursors and stimulate their activity at sites of skeletal remodeling. The temporal coordination of BMP and Wnt signaling is important during fracture healing, as these pathways contribute to the recruitment and differentiation of osteogenic cells and subsequent bone remodeling [44]. Therapeutic strategies targeting components of these pathways are under investigation for selected skeletal disorders; however, their effects on bone repair should not be interpreted as evidence that pathway activity or genetic variation can currently guide rehabilitation decisions [45,46]. These findings underscore the biological relevance of osteogenic signaling pathways to skeletal remodeling and provide a rationale for further research into their potential relationship with rehabilitation outcomes. Their utility for guiding individual rehabilitation decisions, however, remains unestablished.

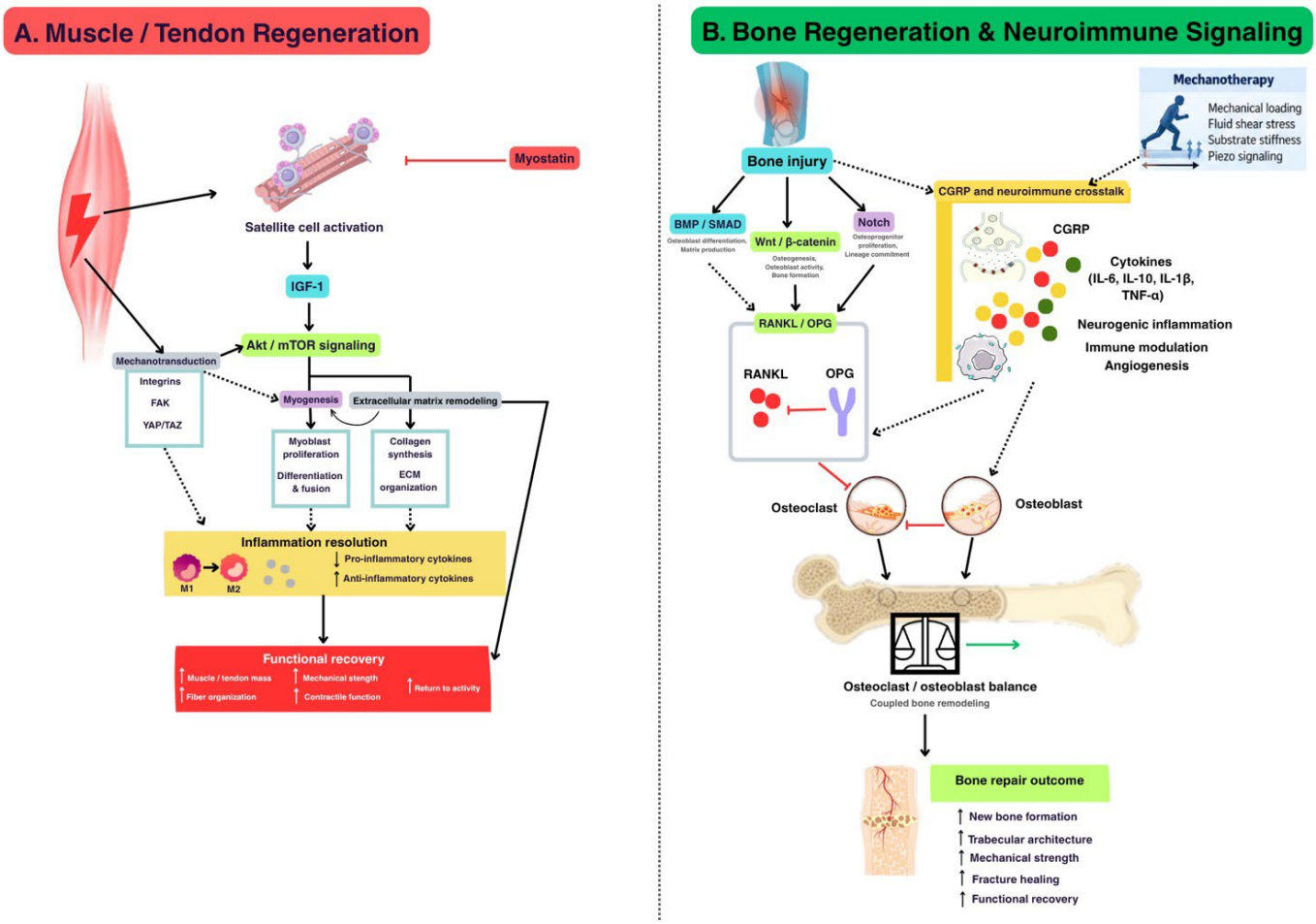


Figure 2. Integrated molecular, neuroimmune, and mechanobiological cascades in musculoskeletal regeneration. (**A**) Muscle and tendon regeneration cascade: Injury triggers satellite cell activation and local IGF-1 release, activating the canonical Akt/mTOR signaling axis. This central node

coordinates mechanotransduction (via integrins, focal adhesion kinase [FAK], and YAP/TAZ), myogenesis (myoblast proliferation, differentiation, and fusion), and extracellular matrix (ECM) remodeling. Bidirectional interactions between myogenesis and ECM remodeling converge on inflammation resolution (transitioning from M1 to M2 macrophage phenotypes with down-regulated pro-inflammatory and up-regulated anti-inflammatory cytokines), ultimately restoring functional muscle/tendon architecture. (**B**) Bone regeneration and neuroimmune signaling: Bone trauma and mechanotherapy (mechanical loading, fluid shear stress) activate key osteogenic pathways (BMP/SMAD, Wnt/β\betaβ-catenin, and Notch) alongside sensory innervation and neuroimmune crosstalk (CGRP release and cytokine modulation). These pathways regulate the osteoblast-osteoclast balance via the RANKL/OPG axis, guiding coupled bone remodeling and structural adaptation. Solid arrows indicate established canonical pathways and well-supported mechanisms; dashed arrows denote proposed, context-dependent, or modulatory links.

3.6. Notch Signaling in Bone Regeneration

Beyond BMP and Wnt pathways, Notch signaling also plays a critical regulatory role in skeletal homeostasis and bone regeneration. Notch signaling influences multiple cellular processes, including proliferation, differentiation, and cell-fate determination, which are essential for coordinated bone repair [47]. In the context of fracture healing, accumulating evidence indicates that Notch signaling interacts closely with BMP pathways and contributes to the regulation of osteoblast differentiation and bone formation. Activation of Notch receptors by their ligands (Jagged and Delta-like proteins) triggers proteolytic cleavage of the receptor and release of the Notch intracellular domain (NICD), which translocates to the nucleus and modulates transcription of genes involved in osteogenic differentiation [47]. Precise regulation of Notch signaling appears to be essential for successful bone regeneration, whereas dysregulation may contribute to pathological conditions such as osteoporosis and delayed fracture healing [47,48]. The effects of Notch signaling on skeletal repair depend on cellular context and the stage of differentiation. Although this pathway is a potential target for further investigation in bone regeneration, evidence is insufficient to establish that its modulation can optimize rehabilitation outcomes or guide treatment selection in patients with musculoskeletal injuries.

3.7. MicroRNAs in Bone Remodeling and Regeneration

MicroRNAs (miRNAs) regulate post-transcriptional gene expression and contribute to osteoblast differentiation, extracellular matrix regulation, and skeletal homeostasis [49]. Members of the miR-29 family, particularly miR-29a, have been implicated in the regulation of extracellular matrix-related processes during bone formation and mineralization [50]. In contrast, an experimental study using rat adipose-derived mesenchymal stem cells (ADSCs) found that miR-146a inhibited osteogenic differentiation through targeting SMAD4, a mediator of BMP-dependent signaling [51]. This finding suggests that miRNA-mediated regulation of BMP/SMAD signaling may influence osteogenic differentiation, although its relevance to bone repair in vivo and in humans requires further investigation. miRNAs also interact with BMP, Wnt/β-catenin, and inflammatory pathways involved in skeletal remodeling [52].

These findings identify miRNAs as potential regulators of skeletal regeneration and candidates for further biomarker and therapeutic research. However, their value for predicting individual healing trajectories or guiding rehabilitation interventions has not been established. Further studies are needed to determine whether specific miRNA profiles are reproducibly associated with clinically meaningful skeletal-repair outcomes.

3.8. Neuroimmune and Cytokine Regulation in Bone Healing

Bone healing involves coordinated interactions among inflammatory cytokines, neuropeptides, immune cells, and osteogenic signaling networks [53]. These interactions influence mesenchymal stromal cell activity, angiogenesis, osteoblast differentiation, and tissue remodeling during skeletal repair. Calcitonin gene-related peptide (CGRP), a neuropeptide associated with sensory innervation, has been implicated in osteogenic signaling in experimental models. In a rat femoral implantation model using an ultrapure magnesium pin, CGRP associated with periosteal sensory fibers and bone marrow was linked to signaling involving cyclic adenosine monophosphate (cAMP) and cAMP response element-binding protein (CREB) [54]. Other in vitro and rodent studies have investigated CGRP-associated mechanisms in tendon–bone and bone–implant integration [55]. These findings support a role for neurogenic signaling in experimental tissue repair, although their implications for human bone healing and rehabilitation outcomes remain uncertain.

The inflammatory response is an integral component of fracture healing and involves cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). TNF-α exhibits temporally and context-dependent effects: early signaling contributes to inflammatory cell recruitment, whereas sustained or excessive activity may impair osteogenic differentiation and tissue repair [56–59]. Conversely, experimental evidence indicates that TNF-α signaling also contributes to normal fracture healing, underscoring the importance of its timing and regulation. IL-1 participates in early inflammatory signaling and has been associated with angiogenesis and callus formation [60]. IL-6 contributes to inflammatory signaling and the recruitment of osteoprogenitor cells during skeletal repair [61]. Although an appropriately regulated inflammatory response supports healing, excessive or prolonged inflammation may disrupt regenerative progression [62]. The resolution of inflammation is also important for the transition toward tissue repair. Cytokines including IL-4, IL-10, and IL-13 can influence macrophage phenotypes and the balance between inflammatory and reparative responses, thereby modulating tissue remodeling and osteogenesis [63]. IL-10 has shown context-dependent effects on bone biology in experimental systems: some in vitro findings suggest that it can promote osteogenesis through p38/MAPK-associated signaling, whereas other findings indicate inhibitory effects under different experimental conditions [64].

Collectively, these findings indicate that skeletal repair depends on interactions among osteogenic, neuroimmune, and inflammatory pathways. However, evidence that these mechanisms influence bone healing in experimental models does not establish that individual neuroimmune profiles predict clinical recovery or identify the optimal rehabilitation strategy. Their potential relevance to functional outcomes and rehabilitation responsiveness requires further investigation (Figure 2).

3.9. Gene Polymorphisms and Muscle Rehabilitation

In addition to the epigenetic and neuroimmune pathways involved in skeletal repair, genetic variation has been investigated as a potential contributor to inter-individual differences in musculoskeletal phenotypes and responses to exercise or treatment [65,66]. Relevant loci include genes involved in extracellular matrix organization, muscle contractile function, anabolic signaling, hormonal regulation, and vitamin D metabolism. However, associations with baseline tissue characteristics or injury susceptibility do not necessarily indicate differences in rehabilitation response. The following sections distinguish the biological functions of these genes from the clinical associations reported in genetic studies and the more limited evidence supporting genotype-guided rehabilitation.

4. Extracellular Matrix and Connective Tissue Integrity

4.1. Collagen Gene Polymorphisms (COL5A1 and COL1A1)

Associations with baseline tissue characteristics or injury susceptibility do not necessarily indicate differences in rehabilitation response. The following sections distinguish the biological functions of these genes from the clinical associations reported in genetic studies and the more limited evidence supporting genotype-guided rehabilitation [67]. Variants in the 3′ untranslated region of COL5A1, including rs12722 and rs13946, have been investigated in relation to connective-tissue characteristics and tendon or ligament injury susceptibility [68,69]. However, reported associations vary across studies and outcomes, and they should not be interpreted as establishing a uniform genetic risk profile.

Such findings are specific to the variants, population, and outcomes studied and do not, on their own, establish a causal effect or a differential response to treatment. As summarized in Table 1, collagen-related variants may help characterize genetic associations with connective-tissue phenotypes, but their clinical utility for rehabilitation remains uncertain. Current evidence does not establish that these variants can reliably determine an individual's mechanical-loading threshold, justify a specific loading progression, or guide the timing and intensity of rehabilitation. Prospective studies testing genotype-by-intervention effects and clinically meaningful functional outcomes are needed before collagen genotyping can be used to guide rehabilitation decisions.

4.2. Myofibrillar Architecture and Contractile Phenotypes

4.2.1. ACTN3 Polymorphism and Muscle Performance

The ACTN3 gene encodes α-actinin-3, a structural protein located at the Z-disc of fast-twitch (type II) muscle fibers, where it contributes to sarcomeric organization during high-force contractions [70]. The common R577X polymorphism (rs1815739; C>T) introduces a premature stop codon, resulting in α-actinin-3 deficiency in individuals with the XX genotype [71]. This deficiency has been associated with differences in muscle-fiber characteristics and metabolic signaling, including greater reliance on oxidative metabolism and altered calcineurin-related signaling in experimental models [72,73].

This variant has been investigated in relation to muscle metabolism, athletic performance, exercise-induced muscle damage, injury epidemiology, and training-related changes in muscle function [74–76]. Although these findings provide a rationale for investigating ACTN3 as a contributor to inter-individual variation in muscle phenotypes and exercise adaptation, results differ across populations, outcomes, and study designs. In particular, associations with athletic performance or baseline muscle characteristics do not establish that ACTN3 genotype predicts recovery after injury or differential benefit from rehabilitation. Current evidence is insufficient to recommend genotype-specific loading progressions, training volumes, intensities, or recovery intervals. ACTN3 genotyping therefore remains investigational for rehabilitation planning, pending prospective studies that directly test genotype-by-intervention effects and clinically meaningful functional outcomes (Table 1).

4.2.2. Myostatin (MSTN) and ACVR2B Polymorphisms

Myostatin (MSTN), a member of the transforming growth factor beta (TGF-β) superfamily, is a negative regulator of skeletal muscle growth that signals through activin type II receptors, including ACVR2B, and downstream SMAD2/3 pathways. The MSTN K153R polymorphism (rs1805086) has been investigated in relation to muscle strength and hypertrophy. In an eight-week resistance-training study involving 94 healthy, previously untrained men, the A55T and K153R variants were associated with changes in muscle

thickness, although the findings were specific to the muscles and genotypes examined [77]. These results provide preliminary evidence that MSTN variation may contribute to differences in training-related muscle adaptation, but they do not establish its value for predicting recovery after injury or disuse.

Separately, a study examining the MSTN A55T variant reported an association with strength recovery following exercise-induced muscle damage [78]. This result is relevant to recovery-related research, but it should not be interpreted as evidence that genotype-guided rehabilitation improves outcomes in patients recovering from clinical injury. Other candidate-gene studies have examined muscle phenotypes in older adults, including associations involving multiple genetic variants [79]. Such findings may help characterize inter-individual variation in muscle characteristics but do not, by themselves, establish a clinically useful prediction of rehabilitation response. Similarly, although ACVR2B participates in myostatin signaling, this biological role does not establish that ACVR2B polymorphisms predict muscle recovery. The reported association between ACVR2B rs2276541 and sarcopenia was not detected in the studied Tibetan population (104). Further prospective studies are needed to establish whether these variants predict clinically meaningful responses to rehabilitation interventions.

Myogenin (MYOG)

Myogenin (MYOG) is a basic helix–loop–helix transcription factor involved in terminal myogenic differentiation and the formation of mature muscle fibers. Experimental evidence indicates that regulatory variation in the MYOG promoter can influence transcription and myogenic processes. For example, the promoter variant rs3471653254 (C>T) has been investigated in studies of porcine muscle development, with findings implicating altered transcriptional regulation in myogenic differentiation [80].

However, evidence from animal and cellular models cannot establish that this variant predicts the rate of muscle regeneration or functional recovery in humans. The available evidence cited here also does not demonstrate that MYOG genotype can be used to determine recovery intervals between rehabilitation sessions. Its potential relevance to human muscle repair and rehabilitation outcomes therefore remains to be established.

Insulin-Like Growth Factor-1 (IGF-1)

Insulin-like growth factor-1 (IGF-1) contributes to skeletal muscle growth and adaptation to mechanical loading. Binding of IGF-1 to its receptor activates downstream signaling, including the PI3K/Akt/mTOR pathway, which supports protein synthesis. Akt signaling also regulates FoxO transcription factors involved in proteolytic pathways, linking anabolic signaling with the control of muscle protein turnover [81,82]. Genetic variation in IGF1 has been investigated in relation to muscle phenotypes and athletic performance. The regulatory-region variant rs35767, for example, has been studied in association with athletic performance, although such associations do not establish a genotype-specific response to rehabilitation [83]. Other reported IGF1 variants should be considered individually, with their effects interpreted according to the specific variant and supporting evidence [84].

Although IGF-1 signaling provides a mechanistic link between loading and muscle adaptation, genetic associations with athletic performance, circulating IGF-1 concentrations, or baseline muscle characteristics do not by themselves establish differential benefit from rehabilitation. Current evidence is insufficient to use IGF1 genotyping to prescribe loading intensity, training volume, or recovery intervals. Prospective intervention studies that directly test genotype-by-treatment interactions are needed before these variants can inform rehabilitation decisions (Table 1).

4.3. Endocrine and Neurometabolic Modulation

4.3.1. Estrogen Receptor-α (ESR1)

Estrogen signaling has been implicated in skeletal muscle maintenance through effects on membrane stability, mitochondrial function, and inflammatory responses to muscle injury [85]. Many of these effects are mediated by estrogen receptor-α (ERα), encoded by ESR1. The ESR1 polymorphism rs2234693 has been investigated in relation to muscle-related outcomes, including exercise-associated soreness, muscle stiffness, and serum creatine kinase levels. In the studied populations, the C allele was associated with selected muscle phenotypes [86] (Table 1). These findings suggest a possible association between ESR1 variation and inter-individual differences in muscle characteristics or responses to exercise. However, they do not establish that the genotype reliably predicts exercise-induced muscle damage or recovery after injury, nor do they support genotype-specific recommendations for recovery duration or anti-inflammatory strategies. The relevance of ESR1 variation to rehabilitation outcomes requires direct investigation in prospective intervention studies.

4.3.2. Vitamin D Pathway Genes (VDR, GC, and CYP2R1)

Vitamin D contributes to musculoskeletal function, calcium homeostasis, and immune regulation. The biological effects of active 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] are mediated in part through the vitamin D receptor (VDR) [87]. VDR polymorphisms, including FokI and BsmI, have been investigated in relation to muscle-fiber characteristics and strength, although associations have varied across studies and populations [88,89].

VDR polymorphisms, including FokI and BsmI, have been investigated in relation to muscle-fiber characteristics and strength, although associations have varied across studies and populations [90]. Variants in GC, including rs4588 and rs7041, and in CYP2R1, including rs10741657 and rs10766197, have been studied in relation to circulating vitamin D concentrations and vitamin D status [91–93] (Table 1). Although these genes are relevant to vitamin D biology, associations with vitamin D status or baseline muscle characteristics do not establish that carriers of particular variants are more susceptible to disuse atrophy or delayed rehabilitation. Nor do they demonstrate that genotype-guided supplementation improves functional outcomes. Decisions about vitamin D testing and supplementation should therefore follow established clinical indications rather than these genetic associations alone.

4.4. Implications for Precision Rehabilitation

Genetic variation in extracellular-matrix proteins, contractile structures, myogenic regulators, endocrine pathways, and vitamin D metabolism has been investigated in relation to musculoskeletal phenotypes and responses to exercise or treatment. However, associations with baseline characteristics, injury susceptibility, pain, or circulating biomarkers should not be assumed to predict differential benefit from rehabilitation.

Interpretation depends on the type of evidence available: a genotype-associated phenotype, a difference in change over time, and a formal genotype-by-intervention interaction support different levels of inference. As summarized in Table 1, much of the evidence remains observational or exploratory, with findings that may vary across populations and outcomes [15,79,86,89,91,93–99]. Current evidence does not establish validated genetic criteria for selecting exercise intensity, loading progression, recovery intervals, or adjunctive supplementation. Prospective studies using appropriate interaction analyses, clinically meaningful outcomes, and independent replication are needed before these markers can guide routine rehabilitation decisions. Table 1 provides

an overview of selected human genetic findings relevant to musculoskeletal phenotypes, highlighting the distinction between reported associations and their potential applicability to rehabilitation decision-making.

Table 1. Human genetic associations relevant to musculoskeletal phenotypes and their translational limits.

Gene and Variant	Study Design and Population	Reported Human Finding	Interpretation for Rehabilitation
COL5A1 rs12722, rs3196378, rs71746744	Brown et al. [95]; British case–control study of Achilles tendon pathology	Associations between COL5A1 and extracellular-matrix regulatory variants and Achilles tendon pathology were investigated. Reported associations were variant- and haplotype-dependent.	Associations with tendon pathology do not establish individual loading thresholds or genotype-specific rehabilitation progression.
COL1A1 rs2249492, rs1800012, rs9898186	Niemiec et al. [15]; prospective cohort of 107 patients with lateral epicondylitis	Selected variants were investigated in relation to pain characteristics and outcomes following platelet-rich plasma treatment.	Associations with pain or treatment outcomes do not establish a reproducible genotype-by-treatment interaction or justify genotype-specific loading prescriptions.
ACTN3 rs1815739 (R577X)	Delmonico et al. [96]; strength-training study in older men and women, *n* = 157	Genotype-associated differences in knee-extensor peak-power response to strength training were investigated.	A training-associated phenotype does not establish that ACTN3 genotype can guide rehabilitation protocols, loading progression, or recovery intervals.
MSTN rs1805086 (K153R)	Kruszewski and Aksenov [77]; systematic review and meta-analysis	The association between the K153R variant and strength- or muscle-mass-related phenotypes in athletes was examined across studies.	Associations with muscle phenotypes do not establish prediction of recovery after injury or disuse.
MSTN A55T	Kim et al. [78]; study of recovery following exercise-induced muscle damage	The variant was investigated in relation to strength recovery following exercise-induced muscle damage.	This recovery-related finding warrants further investigation but does not establish clinical utility for genotype-guided rehabilitation after injury.
ACVR2B rs2276541	Zhang et al. [98]; cross-sectional study of 160 Tibetans	No association between the examined polymorphism and sarcopenia susceptibility was detected in the studied population.	This result does not support use of this variant to predict muscle loss or rehabilitation response.
IGF1 rs35767	Mendes et al. [83]; meta-analysis of studies examining power and endurance athletes	The association between rs35767 and athletic performance was evaluated across studies.	Athletic-performance associations do not establish differential response to rehabilitation interventions.
IGF1-region variant(s)	Kostek et al. [97]; Health, Aging, and Body Composition Study	A polymorphism near IGF1 was investigated in relation to body composition and muscle function in women.	Associations with body composition or muscle function do not by themselves establish treatment-response prediction.

ESR1 rs2234693	Kumagai et al. [86]; study of muscle injury and muscle stiffness	The polymorphism was investigated in relation to muscle-injury and muscle-stiffness outcomes.	These associations do not establish genotype-specific recovery intervals or support genotype-directed anti-inflammatory treatment.
VDR rs1544410 (BsmI), rs2228570 (FokI)	Bahat et al. [89]; study of 120 older men. additional evidence reviewed by Krasniqi et al. [91];	BsmI was associated with leg-extensor strength in one cohort; findings for other vitamin D pathway variants and muscle outcomes have varied across studies.	Current evidence does not validate genotype-specific exercise selection or supplementation dosing.
GC rs4588, rs7041	Nissen et al. [93]: Danish children and adults; evidence also summarized by Krasniqi et al. [91].	Variants were associated with circulating 25-hydroxyvitamin D [25(OH)D] concentrations.	Associations with vitamin D status do not establish effects on functional recovery; genotyping does not replace clinically indicated assessment of vitamin D status.
CYP2R1 rs10741657, rs10766197	Nissen et al. [93]; Danish children and adults	Variants and genetic risk scores were associated with serum 25(OH)D concentrations.	These findings concern vitamin D status, not muscle healing or recovery. Genotype-directed supplementation for rehabilitation remains unestablished.
COMT rs4680	Tammimäki and Männistö [100]; systematic review and meta-analysis of chronic-pain studies	Associations between COMT polymorphism and chronic pain were examined, with findings varying across pain contexts.	Pain-related associations do not establish a basis for changing rehabilitation duration or frequency according to genotype.
BDNF rs6265 (Val66Met)	Baumbauer et al. [101]; study of transition from acute to chronic low-back pain	Genotype and expression were examined in relation to the risk of persistent low-back pain.	Associations with pain persistence do not establish that BDNF genotype predicts differential response to a rehabilitation intervention.
OPRM1 rs1799971 (A118G)	Zlendić et al. [99]; 60 TMD patients. CPIC guideline [102].	Exploratory associations with treatment outcomes, including mouth-opening response, were investigated. CPIC guidance does not support basing opioid dosing on OPRM1 genotype alone.	The reported rehabilitation-related association requires validation. Opioid dosing should not be increased solely on the basis of the OPRM1 G allele.

Note: This table summarizes selected human genetic associations relevant to musculoskeletal phenotypes and rehabilitation. It is not an exhaustive inventory of all genetic findings reviewed. Associations with baseline phenotypes, injury susceptibility, or recovery-related outcomes should not be interpreted as proof of causality or differential treatment response. A predictive effect requires evidence that genotype modifies the response to a defined intervention, preferably demonstrated through a prespecified genotype-by-treatment interaction. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CPIC, Clinical Pharmacogenetics Implementation Consortium; TMD, temporomandibular disorder.

4.5. Cytokine Gene Polymorphisms in Neuromuscular Rehabilitation

Skeletal muscle remodeling following exercise-induced microdamage or traumatic injury involves a coordinated inflammatory response. Genetic variation in cytokine-related pathways has therefore been investigated as a potential contributor to inter-individual differences in inflammatory and muscle-damage responses. A study of older women with obesity examined the IL6 promoter polymorphism −174G>C (rs1800795) in relation to the acute response to eccentric resistance exercise [103]. The interpretation of

genotype-associated differences in cytokine and muscle-damage markers should take into account the study population, exercise protocol, and specific outcomes measured. Although IL-6 participates in exercise-related signaling and muscle adaptation [104], the available evidence does not establish that this variant consistently predicts muscle-regeneration rates or recovery duration.

Polymorphisms in the IL1 gene cluster, including IL1A (+4845), IL1B (+3954, −511, and −3737), and IL1RN (+2018), have also been investigated in relation to inflammatory signaling and muscle-related phenotypes [105]. Acute inflammatory signaling contributes to the initiation of tissue repair, whereas prolonged or dysregulated inflammation may promote catabolic processes and muscle atrophy [106].

However, these biological mechanisms and reported genetic associations do not establish that IL1 genotypes or haplotypes can reliably predict chronic low-grade inflammation or determine the optimal training volume, recovery interval, or use of active-recovery modalities. Prospective intervention studies are needed to establish whether cytokine-related genetic variation meaningfully modifies rehabilitation outcomes.

4.6. Neuromuscular Trophic Signaling: The CNTF-CNTFR Axis

Ciliary neurotrophic factor (CNTF), a member of the IL-6 cytokine family, has been investigated for its role in neuronal maintenance and neuromuscular function. Its receptor, CNTFR, participates in CNTF-related signaling, although the functional consequences of genetic variation in this pathway require careful interpretation. The CNTF 1357G>A variant (rs1800169) has been studied in relation to muscle-function phenotypes. According to the reported evidence, differences in concentric peak torque and muscle-quality measures have been observed across genotypes in some clinical cohorts [107]. Variants in CNTFR, including the promoter variant −1703C>T and the intronic variant 1069T>A, have also been investigated in relation to measures of muscle strength [108,109]. These findings suggest that CNTF–CNTFR-related genetic variation may be associated with selected neuromuscular phenotypes. However, associations with baseline strength or muscle-quality measures do not demonstrate that these variants modify the response to rehabilitation. Current evidence is insufficient to use CNTF or CNTFR genotypes to select high-velocity training, prescribe specific neuromuscular exercises, or determine rehabilitation intensity. Their potential predictive value should be assessed in prospective studies that directly examine genotype-by-intervention effects.

5. Bone Rehabilitation and Gene Polymorphisms: A Precision Approach

Bone healing is a dynamic, stage-dependent process influenced by inflammatory signaling, osteogenic activity, mechanical loading, and individual clinical characteristics. Genetic variants have been investigated in relation to fracture healing, bone mineral density, skeletal remodeling, and other musculoskeletal phenotypes. However, evidence of genetic association does not necessarily indicate that a variant predicts response to rehabilitation or can be used to select a specific loading or weight-bearing protocol. This section examines the reported associations and their potential translational relevance while distinguishing established clinical findings from hypotheses that require prospective validation.

5.1. Nitric Oxide Signaling and Fracture Repair

The *NOS2* gene, which encodes inducible nitric oxide synthase (iNOS), may contribute to fracture-healing variability through pathways involving nitric oxide and

inflammatory regulation. In a preliminary case–control study of 62 adults, the *NOS2* variant rs2297514 was associated with atrophic delayed fracture healing (OR = 3.98, p = 0.015) [110]. A larger case–control study in a Han Chinese population subsequently reported a 38% increase in the odds of fracture non-union associated with the T allele (OR = 1.38, p = 0.0005), with a stronger association in the tibial diaphysis subgroup (OR = 1.77, p = 0.0007) [111]. Complementary evidence from a separate study linked rs2297514 to post-traumatic osteomyelitis susceptibility, with the CC genotype associated with lower susceptibility, although this represents a distinct clinical outcome rather than evidence of fracture non-union [112]. Collectively, these findings support further investigation of *NOS2* variation as a potential marker of fracture-healing heterogeneity. However, no direct evidence currently establishes that genotype-guided prolongation of immobilization or modification of weight-bearing improves outcomes; such rehabilitation decisions should therefore not be based on this variant alone.

5.2. LRP5 and Wnt/β-Catenin Mechanotransduction

The *LRP5* gene encodes a co-receptor in the Wnt/β-catenin signaling pathway and plays an important role in regulating bone formation and bone mineral density (BMD) [113]. The missense variant rs3736228 (p.Ala1330Val) has been associated with lower BMD and a modestly increased risk of osteoporotic fracture in population-based studies [114]. In a separate study of men with idiopathic osteoporosis, the *LRP5* haplotype c.2047A–4037T was associated with higher odds of osteoporosis than the reference haplotype (OR = 3.78, 95% CI 1.27–11.26, $p < 0.001$) [115]. Evidence that *LRP5* variation may modify the relationship between physical activity and BMD further supports investigation of its role in skeletal adaptation to mechanical loading, although the observed associations differed by sex and genotype [116]. These findings provide a biological rationale for studying *LRP5* variants in musculoskeletal rehabilitation; however, current evidence does not establish their utility for individual fall-risk prediction or justify genotype-guided changes in resistance-training intensity, weight-bearing progression, or pharmacological treatment.

5.3. Estrogen Receptor and VDR Pathways

Genetic variation in estrogen receptor and vitamin D receptor pathways has been investigated in relation to skeletal health and selected musculoskeletal outcomes. Variants in ESR1, including rs9322332, have been examined in studies of osteonecrosis and scoliosis-related outcomes, although the specific phenotype and any reported treatment-response association should be interpreted according to the original study [117]. Variants and haplotypes in the vitamin D receptor gene (VDR) have also been investigated in relation to bone health, with findings that may vary across populations and study designs [118,119]. These associations provide a rationale for further research into gene–environment interactions in skeletal health, but they do not establish that genotype-guided supplementation or mechanical-loading strategies improve clinical outcomes. Supplementation and rehabilitation decisions should continue to be based on established clinical indications, bone-health assessment, nutritional status, and individual functional capacity.

5.4. Growth Factors and Master Regulators (FGF, BMP2, RUNX2)

BMP2 and RUNX2 contribute to osteoblast differentiation and bone formation, and genetic variants in these genes have been investigated in relation to skeletal phenotypes [120]. Regulatory variation in the 3′ untranslated region (3′ UTR) of FGF2 has also been examined in relation to predicted miRNA-binding sites and femoral neck bone mineral density [121]. These findings provide evidence of associations between genetic variation and selected skeletal phenotypes, but they do not establish that these variants predict

structural failure during healing or identify patients who would benefit from delayed loading. Decisions about weight-bearing progression should instead be guided by fracture characteristics, healing status, imaging findings, pain, functional assessment, and established orthopedic recommendations.

5.5. Connective Tissue and Joint Stability

Beyond bone, genetic variants in *COL5A1* (rs12722) highlight the interplay between soft tissue laxity and joint stability [122]. Similarly, *COMT* and *ADRB2* polymorphisms are emerging as predictors for chronic temporomandibular joint pain, necessitating a multimodal approach that integrates pain management with targeted neuromuscular retraining [123]. These findings address distinct aspects of musculoskeletal health: connective-tissue characteristics and pain-related phenotypes. Although both may be relevant to rehabilitation assessment, current evidence does not establish that these variants independently determine joint stability or identify which patients will benefit from a specific neuromuscular retraining strategy. Their clinical relevance should be interpreted according to the outcomes measured in the original studies.

5.6. The Pro-Inflammatory Cascade: TNF-α and IL-1 Superfamily

Inflammatory cytokines, including TNF-α and members of the IL-1 family, participate in bone remodeling and the regulation of osteoclast activity. Genetic variants in these pathways have been investigated in relation to bone mineral density (BMD), osteoporosis, and implant-related inflammatory outcomes. The TNF promoter variant −308G>A (rs1800629) has been examined in studies of osteoporosis susceptibility, and a meta-analysis of 15 studies involving 5273 participants reported an association between specific genotype groups and osteoporosis risk [124]. The direction and magnitude of this association should be interpreted according to the genetic model and comparator groups used in the original analysis. TNF-related variants have also been investigated in relation to implant osseointegration, but such findings should not be interpreted as validated tools for predicting implant success or rehabilitation response [125]. The direction and magnitude of this association should be interpreted according to the genetic model and comparator groups used in the original analysis. Variants in IL1A and IL1B, as well as variation in the IL1RN gene, have been investigated in relation to bone mineral density, osteoporotic fractures, and other skeletal outcomes [126–129]. These findings suggest possible associations between inflammatory-pathway variation and selected skeletal phenotypes but do not establish a basis for genotype-guided rehabilitation or reliable individual prediction of treatment outcomes.

The available evidence does not establish the IL1B CC genotype as a consistent predictor of lower lumbar-spine BMD or osteoporotic fracture risk. Variants including IL1A −889C>T, IL1B +3954C>T, and IL1B −511C>T have also been investigated in relation to peri-implant inflammatory diseases [130]. Overall, these findings suggest possible associations between inflammatory-pathway variation and selected skeletal or implant-related phenotypes, but do not establish a basis for genotype-guided rehabilitation or reliable individual prediction of treatment outcomes.

5.7. IL-6 Signaling: Dual Roles in Bone Remodeling and Fracture Vulnerability

IL-6 is a pro-inflammatory cytokine involved in osteoclastogenesis and bone remodeling. The *IL6* promoter polymorphism −174G>C (rs1800795) has been investigated as a potential modifier of BMD and fracture risk, although the reported associations vary across populations and clinical contexts. In postmenopausal women, the G/G genotype has been associated with lower hip BMD and more rapid bone loss in selected subgroups, particularly among women further beyond menopause, those not receiving estrogen

therapy, and those with low calcium intake [131–133]. In a longitudinal cohort of 3376 women aged 65 years or older, G/G carriers also had a higher risk of wrist fracture than C/C carriers; however, no significant association was observed with hip fractures or all non-spine fractures [131]. Conversely, a study of postmenopausal Turkish women found lower BMD values among G/G carriers, although the association between the −174G>C polymorphism and osteoporosis risk did not reach statistical significance, highlighting the uncertainty surrounding its clinical relevance [134]. Collectively, these findings suggest that associations between IL6 variation and skeletal outcomes may depend on hormonal, nutritional, and population-specific factors rather than reflect a consistent, independent genetic determinant of bone loss. Current evidence does not validate IL6 or combined IL6–BGLAP genotypes as biomarkers for clinical risk stratification or justify genotype-guided increases in resistance-training intensity. Exercise prescription and nutritional counseling, including calcium and vitamin D when indicated, should instead be based on established clinical risk factors, bone health, and nutritional assessment.

5.8. The IL-12/IL-23/IL-17 Axis: Autoimmune Arthropathies and Bone Turnover Dynamics

The IL-12/IL-23/IL-17 cytokine axis contributes to immune regulation and has been investigated in relation to inflammatory arthropathies and skeletal remodeling [135]. Variants in IL12B and IL23R have been associated with susceptibility to ankylosing spondylitis (AS) and, in some studies, with disease-activity measures. For example, one study reported an association between the IL12B CC and IL23R AA genotype combination and AS susceptibility, while the IL12B +1188A>C variant (rs3212227) was examined in relation to Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores [136]. In a Bulgarian cohort with rheumatoid arthritis (RA), the IL12B rs17860508 homozygous 22 genotype was associated with disease susceptibility and higher serum IL-23 levels [137]. However, these findings do not establish that the reported variants independently predict the rate of joint damage or response to rehabilitation.

The IL-17 pathway has also been investigated in relation to postmenopausal osteoporosis, including studies of IL17A −197G>A (rs2275913) [138]. Although these findings may help characterize genetic contributions to inflammatory and skeletal phenotypes, they do not justify genotype-based prescriptions for joint-sparing exercise, aquatic therapy, or the timing and intensity of mechanical loading. Rehabilitation for inflammatory arthropathies should be individualized according to disease activity, joint involvement, bone health, functional status, and the patient's medical treatment, rather than these genotypes alone.

6. Genetic Modulation of Pain and Rehabilitation Outcomes: A Precision Framework

The transition from acute to chronic musculoskeletal pain is influenced by multiple biological, psychological, and clinical factors. Genetic variation may contribute to inter-individual differences in pain processing and symptom persistence, but its relevance to rehabilitation outcomes and treatment selection remains incompletely established. This section reviews genetic findings related to pain phenotypes while distinguishing biological plausibility and observational associations from evidence that genotype modifies the response to a specific intervention.

6.1. Neurotransmitter and Opioid Pathways: COMT, BDNF, and OPRM1

The COMT gene, which encodes catechol-O-methyltransferase and contributes to catecholamine metabolism, has been investigated in relation to pain sensitivity and chronic musculoskeletal pain. The Val158Met variant (rs4680), which affects COMT

enzymatic activity, has been studied in conditions including fibromyalgia, temporomandibular disorders, and chronic low back pain, although associations vary across populations and clinical phenotypes [100,139,140]. In a surgical cohort, COMT haplotypes associated with lower enzymatic activity were reported to be related to postoperative pain intensity and functional recovery one year after lumbar discectomy [141].

The BDNF Val66Met variant (rs6265) has been investigated in relation to activity-dependent synaptic plasticity and pain-related phenotypes. Although reduced activity-dependent BDNF secretion provides a potential mechanistic link, the direction and clinical relevance of associations with pain vary by condition and study design [101]. Variants in opioid-receptor genes, including OPRM1 rs589046 and OPRD1 rs2234918, have also been examined in relation to pain sensitivity and conditioned pain modulation in patients with hip osteoarthritis [142]. These findings may contribute to understanding inter-individual variation in pain processing, but do not establish reliable genotype-based predictions of response to physical rehabilitation or other pain treatments.

6.2. Nociceptive Phenotyping: ANK2, GDF5, and FAAH

Emerging genomic evidence suggests that genetic variation may contribute to differences in sensory phenotypes. In a genome-wide association analysis, the ANK2 variant rs72669682 was significantly associated with the distinction between "irritable" and "non-irritable" nociceptor profiles in a cohort with neuropathic pain, identifying ANK2 as a candidate locus for further investigation in sensory phenotyping [143]. However, this finding relates to sensory phenotyping in neuropathic pain and does not establish an association with musculoskeletal disorders or musculoskeletal rehabilitation outcomes. Its relevance to precision musculoskeletal rehabilitation therefore remains to be investigated.

Similarly, GDF5 rs143384 has been associated with chronic postsurgical pain in a Han Chinese case–control study, although the association varied across clinical subgroups [144]. Separately, rs143384 has shown BMI-dependent associations with knee osteoarthritis risk, being associated with a reduced risk in obese individuals but an increased risk in non-obese individuals [145]. These findings suggest that genetic associations may vary across clinical outcomes and population subgroups; however, they do not establish that GDF5 genotype predicts rehabilitation response. The FAAH gene, including the rs324420 (C385A) variant, has been investigated in relation to endocannabinoid signaling and pain-related phenotypes. Associations with pain perception or exercise-related symptoms should be interpreted according to the population and outcome assessed in each study [146,147]. In particular, differences in pain tolerance should not be equated with differences in tissue damage or susceptibility to overtraining. Current evidence is insufficient to use FAAH genotype to prescribe exercise intensity, predict exercise-induced muscle injury, or determine recovery intervals.

6.3. Genetic Variation in miRNA-Related Loci

Beyond protein-coding genes, miRNAs regulate post-transcriptional gene expression and have been investigated in relation to bone mineral density (BMD) and fracture-related phenotypes. Variants in or near miRNA-related loci, including rs6430498 in miR-3679 and rs12512664 in miR-4274, have been associated with femoral-neck BMD or fracture risk in genetic studies [148]. These findings may help identify regulatory pathways involved in skeletal health, but genetic associations with BMD or fracture risk do not establish that these variants predict response to rehabilitation. Further research is required before miRNA-related genetic variation can be considered for individual risk prediction or for selecting loading and weight-bearing protocols.

6.4. Serotonergic and Other Pain-Related Genetic Associations

Genetic variation in pain-related pathways may contribute to inter-individual differences in pain perception, symptom severity, and related clinical phenotypes. Variants in opioid-receptor genes, including OPRM1 and OPRD1, have been associated with pain sensitivity in patients with hip osteoarthritis [142], while HTR2A polymorphisms have been investigated in relation to chronic low back pain and disability [149]. However, these associations do not establish that genetic variants modify the effects of specific rehabilitation interventions.

At present, genetic findings in pain-related pathways are best regarded as potential contributors to biological heterogeneity rather than stand-alone tools for selecting rehabilitation treatments. Their clinical utility will depend on prospective validation, reproducibility across populations, and demonstration that incorporating genotype improves outcomes beyond established clinical assessment. Until such evidence is available, rehabilitation decisions should be based primarily on pain phenotype, functional status, comorbidities, patient goals, and response to treatment, with genetic information considered investigational rather than prescriptive.

7. Genetic Variation and Responsiveness to Rehabilitation and Regenerative Interventions

7.1. Physical Rehabilitation Modalities and Molecular Adaptation

Rehabilitation interventions differ in their primary stimuli and proposed biological effects. Exercise and mechanical loading provide central stimuli for functional adaptation, whereas modalities such as electrical stimulation, heat therapy, and massage have been investigated for their effects on neuromuscular activity, inflammatory signaling, and tissue recovery. Biological and regenerative interventions, including platelet-rich plasma (PRP), represent a distinct group of approaches and are considered separately below. Across these intervention types, evidence that a treatment alters a molecular pathway should be distinguished from evidence that a genetic variant modifies the clinical response to that treatment.

7.1.1. Electrotherapy and Regeneration-Associated Gene Expression

Electrical stimulation is used in rehabilitation to manage pain and support functional recovery in selected musculoskeletal and neurological conditions, although clinical effectiveness varies by modality and indication [150,151]. Experimental studies indicate that electrical stimulation can influence axonal regeneration and neuroplasticity-related pathways; however, the extent to which these effects generalize across musculoskeletal tissues and routine physiotherapy protocols remains uncertain [151–153]. In a peripheral nerve injury model, the BDNF rs6265 variant was associated with an attenuated regenerative response to electrical stimulation. This finding raises the possibility that genetic variation may contribute to interindividual differences in responsiveness, but it does not establish a clinically actionable genotype-by-treatment interaction. Clinical validation is therefore required before genetic information can be used to guide electrotherapy selection or dosing.

7.1.2. Heat Therapy, Epigenetic Regulation, and Skeletal Muscle Adaptation

Thermal interventions have emerged as potential modulators of skeletal muscle metabolism and adaptive signaling. Heat therapy has been reported to attenuate skeletal muscle atrophy and preserve plantar flexor strength in healthy individuals, partly through suppression of the FoxO and NF-κB signaling pathways implicated in proteolysis and inflammatory catabolism [154]. Furthermore, passive muscle heating increases the

phosphorylation of Akt, mTOR, 4E-BP1, and ribosomal protein S6 (RPS6), all of which are central regulators of protein synthesis, cellular proliferation, and survival in skeletal muscle [155]. In addition to these anabolic effects, thermal exposure may induce epigenetic modifications that influence long-term physiological adaptation. DNA methylation, histone remodeling, and non-coding RNA expression have all been implicated in heat-induced cellular responses [155,156].

For instance, miR-297 expression increases during heat acclimatization in rodents, whereas DNA methyltransferase 3A (DNMT3A) expression increases during heat stress and decreases under cold exposure. Moreover, post-translational histone modifications have been implicated in heat acclimation-mediated cytoprotective memory, while studies of heat-acclimation memory suggest that residual transcriptomic changes during deacclimation may facilitate rapid reacclimation and cytoprotection [157,158]. Together, these findings support the possibility that thermal exposure induces persistent molecular adaptations; however, whether similar mechanisms are elicited by clinical thermal rehabilitation and contribute to interindividual differences in treatment responsiveness remains uncertain.

7.1.3. Massage Therapy and Inflammatory Gene Modulation

Massage therapy has also been associated with molecular alterations relevant to tissue recovery and inflammation control. Compared with non-massaged skeletal muscle, massaged tissue demonstrates reduced NF-κB activity and increased expression of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a key regulator of mitochondrial biogenesis and oxidative metabolism [159]. These molecular findings suggest potential effects on inflammatory and metabolic pathways involved in tissue adaptation. However, whether these changes translate into clinically meaningful improvements in musculoskeletal recovery remains uncertain.

7.2. PRP and Genetic Variation in Treatment Response

PRP is an autologous blood-derived preparation obtained by processing whole blood to produce a platelet-enriched fraction [160]. Its composition may include variable amounts of plasma, leukocytes, residual erythrocytes, and soluble signaling molecules. Following activation, platelets release mediators, including platelet-derived growth factors (PDGFs), transforming growth factor-β (TGF-β), and vascular endothelial growth factor A (VEGFA), which participate in inflammatory signaling, cell recruitment, angiogenesis, and extracellular-matrix remodeling [161]. These biological properties have motivated the investigation of PRP in musculoskeletal and regenerative medicine [160,161]. However, PRP is not a uniform intervention: its composition and biological activity vary with preparation and activation methods, while clinical outcomes may also depend on the indication and administration protocol [160,162].

PRP should also be distinguished from other autologous blood-derived preparations, including autologous conditioned serum, autologous protein solutions, and platelet-rich fibrin. These products differ in preparation methods, cellular composition, and concentrations of soluble mediators and should not be assumed to have equivalent biological effects [163,164]. Bone marrow aspirate concentrate is derived from a different tissue source and represents a distinct intervention [163]. Accordingly, evidence concerning genetic variation in response to PRP should not automatically be generalized to other autologous biological therapies.

The potential relationship between host genotype and PRP response involves several distinct processes. Genetic variation may be associated with baseline tissue properties, inflammatory responses, extracellular-matrix organization, or tissue-repair capacity [15]. Variants in genes encoding growth factors or their receptors, including *PDGFA*, *PDGFB*,

and *PDGFRB*, have also been examined in studies of outcomes following PRP administration [16,19]. However, an association with a baseline phenotype does not necessarily indicate altered responsiveness to PRP, and the functional consequences of a variant cannot be inferred from the identity of the gene alone. Demonstrating a treatment-specific genetic effect requires evidence that outcomes differ by genotype between appropriately compared treatment groups, ideally through a prespecified genotype-by-treatment interaction analysis [165].

In lateral elbow tendinopathy, several studies have examined associations between specific genetic variants and clinical outcomes following PRP administration. For *COL1A1*, variants were associated with differences in pain characteristics, although their influence on overall PRP treatment effectiveness appeared limited [15]. Studies of platelet-derived growth factor-related genes have reported associations between selected genotypes and clinical outcomes after PRP treatment. For *PDGFA*, the A allele of rs1800814 and the T allele of rs2070958 were associated with better outcomes on selected measures, whereas the GG and CC genotypes, respectively, were associated with a greater need for additional manual or physical therapy [17].

For *PDGFB*, the TT genotype of rs2285099, the CC genotype of rs2285097, and the AA genotype of rs2247128 were associated with better outcomes on selected pain and functional measures [16]. Studies of *PDGFRB* have likewise reported associations between the CC genotype of rs3828610 and the GG genotypes of rs3756311 and rs3756312 and selected clinical outcomes [19,166]. These findings are preliminary, and proposed explanations involving platelet characteristics, receptor activity, or regenerative signaling should be considered hypotheses unless directly demonstrated.

Variants in *VEGFA*, which encodes vascular endothelial growth factor A, have also been investigated in relation to tendon pathology and outcomes following PRP administration. In patients with tennis elbow, the GG genotype of rs2010963 and the CC genotype of rs3024998 were associated with better outcomes on selected measures during follow-up [20,167]. Separately, the A-G-G haplotype comprising rs699947, rs1570360, and rs2010963 was associated with susceptibility to Achilles tendinopathy [168]. This distinction is important because genetic susceptibility to tendon pathology does not necessarily predict response to treatment. Although VEGF signaling contributes to angiogenesis and tissue repair, its effects may vary according to tissue context and the timing and duration of signaling [169].

Evidence concerning intra-articular PRP should be considered separately from studies of tendon disorders. In knee osteoarthritis, an observational study comparing intra-articular hyaluronic acid, PRP combined with hyaluronic acid, and peripheral blood mononuclear cell injections reported improvements in several clinical outcomes over six months, although the study did not establish the superiority of one treatment across all outcomes [170]. A systematic review and meta-analysis of 28 randomized controlled trials involving 3246 patients also evaluated the efficacy and safety of PRP injections for knee osteoarthritis, reporting outcome differences across comparators and treatment protocols [171]. These studies provide clinical context for intra-articular PRP but do not establish whether genetic variation modifies treatment response. Findings from tendon-related studies therefore cannot be directly extrapolated to knee osteoarthritis, and evidence supporting genotype-guided selection of patients for intra-articular PRP remains insufficient.

These findings should be interpreted cautiously. The reports largely derive from a shared research programme involving 107 patients and 132 treated elbows and therefore should not be considered independent replications in separate populations. Furthermore, associations between genotype and outcomes among PRP-treated patients do not, on their own, establish a genotype-specific benefit of PRP relative to another treatment.

Independent prospective studies incorporating appropriate comparators, prespecified genotype-by-treatment interaction analyses, and adequate control for multiple comparisons are needed before these candidate associations can inform clinical decisions. At present, the evidence does not support routine genetic testing to select patients for PRP treatment.

8. Genetic Integration with Minimally Invasive Musculoskeletal Interventions

The molecular pathways investigated in minimally invasive musculoskeletal interventions overlap with those implicated in genetic studies of muscle adaptation, connective-tissue remodeling, bone turnover, inflammation, and pain processing. These include the IGF-1/PI3K/Akt/mTOR axis involved in muscle anabolism, myostatin-related regulation of muscle growth, extracellular-matrix remodeling in tendon and ligament healing, and BMP/SMAD and Wnt/β-catenin signaling in osteogenesis. Variants in inflammatory and pain-related genes, including IL1B, IL6, TNF, COMT, BDNF, and OPRM1, have also been investigated in relation to musculoskeletal phenotypes and pain-related outcomes. However, evidence linking a genetic variant to a baseline phenotype or molecular pathway does not, by itself, demonstrate that the variant modifies the clinical effect of an injection-based or other minimally invasive intervention [172,173].

The potential relevance of these variants to treatment selection remains a research question. Establishing clinical utility would require appropriately designed studies that compare treatment effects across genotype groups, preferably using prespecified genotype-by-treatment interaction analyses and suitable comparator groups. Such studies should also account for relevant clinical characteristics, intervention protocols, and population-specific genetic variation, followed by independent replication. Until these requirements are met, genetic findings should be interpreted as evidence of possible biological heterogeneity rather than as a basis for selecting injection type, dose, timing, or adjunctive rehabilitation. Current clinical decisions should continue to be guided by the patient's diagnosis, disease severity, functional status, comorbidities, treatment goals, and observed response to care. Table 2 summarizes human studies examining genetic associations with adaptations to structured exercise or outcomes following musculoskeletal interventions, with particular attention to study design, reported response patterns, and the limitations of their translational interpretation.

Table 2. Human studies relating genetic variation to exercise adaptation or musculoskeletal treatment outcomes.

Locus and Source	Design and Population	Intervention or Exposure	Supported Findings	Evidence Boundary
ACTN3 rs1815739 Clarkson 2005 [174]	Pre/post training cohort; 247 men and 355 women (n = 602).	12-week unilateral upper-arm resistance training.	Women with XX had greater dynamic strength gains than RR; no association in men. Genotype explained about 2% of strength-gain variation.	Small, sex-specific contribution. No genotype-tailored programme was tested.
ACTN3 rs1815739 Delmonico 2007 [96]	Pre/post training cohort; 71 older men and 86 older women (n = 157).	Approximately 10 weeks of unilateral knee-extensor training.	RR women had greater relative peak-power improvement than XX women; the comparison in men was not statistically significant.	These reports cannot support a universal favourable *ACTN3* genotype.

MSTN A55T; K153R Li 2014 [175]	Pre/post training cohort; 94 healthy, untrained Han Chinese men.	8-week strength-training programme; ultrasound muscle thickness.	A55T Thr carriers had greater biceps-thickness gain; the quadriceps result was not significant. K153R heterozygotes had greater gains in both muscles.	Candidate associations in healthy men. Does not establish optimal load, clinical recovery or hypertrophy prediction in patients.
MSTN A55T rs1805085 Kim 2020 [78]	Acute exercise cohort; 48 healthy Korean men; Ala/Ala = 34, Ala/Th r= 13, Thr/Thr = 1.	50 maximal eccentric contractions; strength and damage-marker recovery.	Ala/Thr participants recovered isometric strength faster than Ala/Ala. Soreness, CK and AST did not differ significantly.	Very small genotype subgroups; strength recovery is not equivalent to tissue regeneration. No dosing algorithm was evaluated.
IGF1 Promoter CA repeat Kostek 2005; Sood 2012 [176,177]	Two pre/post cohorts of older adults: *n*= 67 and *n* = 114.	10-week unilateral knee-extensor training; 192-bp repeat allele.	192-bp carriers gained more strength in (176), but genotype did not predict peak-power change in (177). Hypertrophy was not significant in (176).	A microsatellite, not rs35767. Findings are endpoint-dependent; do not extrapolate them to SNP-specific tendon rehabilitation.
CNTF 1357 G>A Walsh 2009 [107]	Pre/post training cohort; 754 healthy young White adults; 40% men.	12-week unilateral upper-arm resistance training.	GG women gained more trained-arm isometric strength than A-allele carriers; no significant association in men or muscle cross-sectional area.	Sex-specific and small contribution. A hypothesis for neuromuscular adaptation, not a validated training prescription.
IL6 rs1800795 Funghetto 2013 [103]	Acute exercise cohort; 90 older women with obesity.	7 sets of 10 eccentric repetitions at 110% of 10RM; sampling over 48 h.	CK rose at 24–48 h in GG; CC/CG had higher immediate post-exercise IL-6. Effects concerned biochemical responses.	No heat therapy, long-term function or genotype-directed recovery interval was tested.
PDGFB rs2285099; rs2285097; rs2247128 Niemiec 2021 [16]	Prospective treated cohort; 107 patients, 132 elbows; Polish recruitment programme.	Autologous PRP for lateral elbow tendinopathy; 52-week follow-up.	TT/CC at the first two loci and AA at rs2247128 had better pain/disability scores at selected time points; platelet traits also differed.	Exploratory outcome associations. Linkage disequilibrium, concomitant treatment and cohort overlap limit interpretation.
PDGFA rs1800814; rs2070958 Jarosz 2022 [17]	Prospective treated cohort; 107 patients, 132 elbows; shared programme.	PRP; 104-week follow-up.	A-allele and T-allele carriers, respectively, had better PROMs mainly during early follow-up; other genotypes more often received additional therapy.	No independently validated selection rule; additional therapy complicates attribution of recovery to PRP.
PDGFRB rs3828610; rs3756311; rs3756312 Szyluk 2022 [19]	Prospective treated cohort; 107 patients, 132 elbows; shared programme.	PRP; 104-week follow-up.	CC at rs3828610 and GG at rs3756311/rs3756312 were associated with favourable PROMs; mean platelet volume also differed.	Associations do not prove receptor-promoter mechanisms or genotype-specific PRP benefit versus a comparator.
PDGFRA rs6554164; rs1316926; rs7668190 Jarosz 2024 [18]	Prospective treated cohort; 107 patients; shared programme.	PRP; 104-week follow-up; PROMs and MCID.	T-allele carriers at rs6554164 and AA at rs1316926/rs7668190 had more favourable outcomes.	No standardized post-injection rehabilitation protocol; external replication is required before patient selection.

VEGFA rs2010963; rs3024998 Niemiec 2023 [20]	Prospective treated cohort; 107 patients, 132 elbows; shared programme.	PRP; 104-week follow-up.	GG at rs2010963 and CC at rs3024998 were associated with better pain/disability outcomes.	PROM evidence, not a measured genotype effect on neovascularization or healing rate. No treatment-interaction validation.
COL1A1 rs2249492; rs1800012; rs9898186 Niemiec 2024 [15]	Prospective treated cohort; 107 patients; shared programme.	PRP; 104-week follow-up; pain phenotype and treatment outcomes.	Variants were associated with pain characteristics, but did not substantially influence treatment effectiveness; a modest rs35231764 signal was noted.	Predominantly null response finding. A pain-risk marker is not automatically a PRP-response marker.
COMT/OPRM1 rs4680; rs4646310/rs1799971 Zlendić 2024 [99]	Prospective treatment cohort; 60 TMD patients (55 women, 5 men).	Education, home physical therapy and occlusal splint; 6 months.	Selected COMT minor alleles were associated with less pain reduction; OPRM1 minor-allele carriage predicted poorer pain-free mouth-opening response.	Small, predominantly female sample receiving multimodal care. Does not validate genotype-specific exercise or opioid dosing.

Abbreviations: 10RM, ten-repetition maximum; AST, aspartate aminotransferase; CK, creatine kinase; MCID, minimal clinically important difference; PROMs, patient-reported outcome measures.

9. Limitations

Several limitations should be considered when interpreting the findings of this scoping review. First, the available evidence was heterogeneous in terms of study populations, genetic variants, rehabilitation modalities, intervention parameters, and outcome measures. This heterogeneity limits direct comparisons across studies and makes it difficult to draw consistent conclusions regarding the clinical relevance of individual genetic associations. In addition, the strength of evidence varied across research domains, with some findings supported primarily by mechanistic or preclinical studies and others investigated in clinical populations. Consequently, biological plausibility should not be interpreted as evidence of clinical utility, and associations between genetic variants and recovery outcomes should be distinguished from demonstrated genotype-by-intervention effects. Second, the extent to which reported associations are reproducible across populations and rehabilitation settings remains uncertain. Differences in genetic background, clinical characteristics, environmental exposures, and intervention protocols may contribute to variation in reported findings. Moreover, the limited availability of independently replicated genotype-by-intervention analyses and prospective evaluations of genotype-guided rehabilitation restricts conclusions about the current readiness of genetic information for clinical decision-making. Finally, as a scoping review, this study was designed to map the available evidence and identify research gaps rather than to estimate pooled intervention effects or establish the certainty of evidence for specific clinical recommendations. The findings should therefore be interpreted as a characterization of the current research landscape rather than as confirmation that genetic testing can reliably guide rehabilitation selection, intensity, or dosing. Future research should prioritize adequately powered and independently replicated studies, prespecified genotype-by-intervention analyses, standardized outcome measures, and prospective evaluation of whether genotype-guided rehabilitation improves patient outcomes.

10. Conclusions and Future Directions

This review underscores the potential of incorporating genetic and epigenetic profiling into the paradigm of precision musculoskeletal rehabilitation. The therapeutic response of skeletal muscle, bone, and connective tissues to physical exercise, mechanical

loading, thermal modalities, and regenerative interventions (such as PRP) is modulated by complex gene–environment interactions. Key polymorphic variants in growth factors, matrix metalloproteinases, cytokines, and pain receptors contribute significantly to the interindividual variability observed in clinical outcomes. Transitioning from a conventional, standardized rehabilitation model to a genotype-informed framework offers the potential to optimize recovery trajectories, mitigate injury risks, and refine the prescription of both physical and minimally invasive intervention. However, the clinical translation of these findings is currently limited by the predominantly associative nature of existing candidate-gene studies, small cohort sizes, and a lack of standardized, multi-omic clinical trials. Future research should prioritize large-scale, prospective genome-wide association studies and integrated epigenetic analyses to validate robust genetic markers. Developing validated clinical decision algorithms that combine genetic stratification with functional phenotypic assessments will be essential to establish precision rehabilitation as a standard of care in musculoskeletal medicine.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jpm16110569/s1, Supplementary Table S1. Characteristics of the included studies and their relevance to musculoskeletal rehabilitation; Supplementary Table S2. Full search strategies per database; Supplementary Table S3. Part 1. Exercise training and acute exercise responses. Part 2. Observational, pain-susceptibility, pharmacogenetic, and secondary evidence. Part 3. PRP treatment-response reports from one shared cohort. Part 4. TMD pain and conservative treatment; PRISMA ScR Reporting Checklist [178].

Author Contributions: M.H.: Conceptualization, Writing—Original Draft; S.D.: Writing—Original Draft; M.H.T.: Writing—Original Draft; N.K.: Writing—Original Draft; S.R.M.: Writing—editing and reviewing, Visualisation; B.F.: Conceptualization; A.J.: Conceptualization, Writing—Original Draft, Writing—editing and reviewing, Supervision, Project Administration. This paper is submitted with the agreement of all its co-authors and all authors have approved the author list. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethics and Consent to Participate declarations: Not applicable. This manuscript is a review article and did not involve human participants, human-derived samples, or experimental animals.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: The authors would like to thank the Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), Iran University of Medical Sciences, Tehran, Iran, for their scientific support throughout the period of study. The authors acknowledge the use of Chatgpt and Grammarly solely for language and readability assistance during manuscript preparation. These tools did not replace the authors' scientific judgment and were not used for evidence selection, data extraction or analysis, or development of conclusions. All authors reviewed and edited the final text and take full responsibility for its content. The authors used Canva for design and layout. All visual elements were manually selected, generated, arranged, and reviewed by the authors. No generative AI tools were used to automatically create or alter the scientific content or imagery. The final figure is the original work of the authors, who take full responsibility for its content and accuracy.

Conflicts of Interest: The authors declare no competing interests that may have influenced in this manuscript.

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