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ACE I/D AND ACTN3 R577X POLYMORPHISMS IN SKELETAL MUSCLE RECOVERY AND HYPERTROPHIC ADAPTATION DURING POST-OPERATIVE REHABILITATION: A NARRATIVE REVIEW

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ABSTRACT

Background: Skeletal muscle loss and impaired muscle function are common consequences of surgery, particularly when recovery involves immobilisation, pain, reduced physical activity, and prolonged limited mechanical loading. Progressive rehabilitation can substantially restore muscle strength and mass, yet individuals often respond differently to apparently similar rehabilitation programmes. Genetic variation has therefore attracted interest as one possible contributor to inter-individual differences in muscular adaptation. Among the most extensively investigated variants are the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism and the α-actinin-3 (ACTN3) R577X polymorphism.

Objective: This narrative review examines the potential relevance of ACE I/D and ACTN3 R577X polymorphisms to skeletal muscle recovery, strength restoration, muscle damage, and hypertrophic adaptation during postoperative rehabilitation.

Methods: Relevant literature examining ACE and ACTN3 polymorphisms, skeletal muscle phenotypes, resistance-training adaptations, exercise-induced muscle damage, immobilisation, and postoperative rehabilitation was considered. Particular emphasis was placed on systematic reviews, meta-analyses, longitudinal resistance-training studies, and mechanistic investigations.

Results: The available evidence suggests that ACE and ACTN3 are biologically relevant to skeletal muscle phenotypes, but their effects are neither large nor sufficiently consistent to support their use as independent predictors of postoperative recovery. ACTN3 R577X is associated with the expression of α-actinin-3 in fast skeletal muscle fibres, and recent meta-analytic evidence indicates associations with selected measures of maximal strength, maximal voluntary contraction, and jumping performance. However, findings concerning hypertrophic responses to resistance training have been inconsistent. Similarly, ACE I/D has been associated with physical-performance phenotypes in some populations, but studies of resistance training have not consistently demonstrated genotype-dependent differences in muscle hypertrophy. Evidence regarding ACTN3 and exercise-induced muscle damage is also mixed, with stronger indications of genotype-related effects during prolonged, high-volume endurance exercise than during resistance exercise.

Conclusion: ACE I/D and ACTN3 R577X may contribute to individual variation in skeletal muscle characteristics and exercise adaptation, but current evidence is insufficient to establish either polymorphism as a determinant of postoperative muscle recovery or hypertrophy. Future research should investigate these variants prospectively in surgical populations while simultaneously accounting for rehabilitation dose, age, sex, nutritional status, baseline muscle characteristics, adherence, and surgical factors. Genotype-guided rehabilitation remains a promising research concept rather than an established clinical practice.

KEYWORDS: ACE I/D; ACTN3 R577X; skeletal muscle; postoperative rehabilitation; muscle hypertrophy; muscle recovery; resistance training; exercise genetics; precision rehabilitation

1. INTRODUCTION

Recovery of skeletal muscle following surgery is not simply a matter of waiting for the surgical site to heal. Changes in muscle size, strength and neuromuscular function can occur rapidly when normal mechanical loading is interrupted. Pain, swelling, immobilisation, reduced physical activity and restrictions on weight-bearing or joint movement can collectively create an environment in which muscle protein breakdown exceeds muscle protein synthesis. These changes may compromise mobility and prolong the return to normal physical function.

The problem is particularly relevant following orthopaedic procedures. Patients undergoing procedures such as total knee arthroplasty, hip replacement or ligament reconstruction may enter rehabilitation with substantial deficits in muscle strength and physical function. These deficits can persist even when conventional rehabilitation is provided. Recent evidence indicates that adding appropriately progressed resistance exercise to standard postoperative rehabilitation can produce greater improvements in muscle strength and muscle mass than standard rehabilitation alone (Monsegue et al.,

2024). Similarly, evidence from immobilisation and disuse studies indicates that resistance exercise can attenuate losses in muscle volume and function (2025).
Although rehabilitation is effective, recovery is not uniform. Two patients undergoing similar procedures and receiving broadly comparable rehabilitation may achieve different levels of muscle strength and hypertrophy. Several factors may account for this variation, including age, sex, previous training status, nutritional intake, sleep, psychological factors, disease burden, rehabilitation adherence and the magnitude of the initial surgical insult. Genetic variation represents another possible contributor.
Interest in exercise genetics has particularly focused on the angiotensin-converting enzyme (ACE) gene and the α-actinin-3 (ACTN3) gene. The ACE I/D polymorphism involves an insertion or deletion variant, whereas ACTN3 R577X is a nonsense polymorphism that can result in complete absence of functional α-actinin-3 in individuals with the XX genotype. These variants are attractive candidates because their biological functions intersect with processes important to physical performance. ACE is part of the renin–angiotensin system and is involved in vascular and metabolic regulation. ACTN3 encodes a structural protein located predominantly in fast skeletal muscle fibres and is closely related to muscle contractile properties.
The literature, however, requires careful interpretation. ACE and ACTN3 have been studied predominantly in relation to athletic performance, baseline muscle characteristics and responses to exercise in healthy individuals. These findings cannot automatically be transferred to patients recovering from surgery. Indeed, a recent meta-analytical review found considerable heterogeneity in studies of ACE and ACTN3 and emphasised that the effects of these variants are modest relative to the multifactorial nature of athletic performance (2025).
The distinction is particularly important in postoperative rehabilitation. The relevant question is not whether a genotype is associated with being a strong or powerful athlete. Rather, the clinically meaningful question is whether genotype modifies the trajectory of muscle loss and recovery after surgery or alters the magnitude of adaptation to a prescribed rehabilitation stimulus.
This review therefore examines the biological and empirical evidence linking ACE I/D and ACTN3 R577X to skeletal muscle recovery and hypertrophic adaptation, with particular attention to the implications for postoperative rehabilitation.

2. Postoperative Skeletal Muscle Loss and the Need for Progressive Rehabilitation

Surgical recovery is accompanied by a period of reduced physical activity that can have significant consequences for skeletal muscle. Mechanical unloading itself is a potent stimulus for muscle atrophy. Even relatively short periods of disuse can reduce muscle protein synthesis, muscle fibre size and neuromuscular performance.
This issue is particularly important following orthopaedic surgery because the operated limb may receive substantially less mechanical loading than the contralateral limb. The resulting decline in muscle function can create a cycle in which weakness limits physical activity, reduced activity promotes further muscle loss, and muscle loss makes subsequent rehabilitation more difficult.
A recent review of unloading-induced muscle wasting emphasised that relatively short periods of mechanical unloading can produce rapid skeletal muscle atrophy and reductions in physical capacity (2024). The authors also highlighted the importance of mechanical loading as a target for both preventing muscle loss and facilitating subsequent recovery.
Resistance exercise represents one of the most effective methods of restoring muscle function because it provides a direct mechanical stimulus for adaptation. Resistance exercise increases muscle protein synthesis, and repeated bouts of exercise over time contribute to increases in muscle mass (2015).
Evidence is also emerging specifically from postoperative rehabilitation. Monsegue et al. (2024) concluded that resistance exercise-based rehabilitation following total knee arthroplasty can produce greater improvements in muscle strength and muscle mass than standard rehabilitation. The benefits also extend to functional outcomes such as stair climbing and chair-standing performance.
These observations establish the physiological context in which genetic differences could potentially become relevant. If individuals differ in their muscle fibre characteristics, contractile properties or response to mechanical loading, it is reasonable to ask whether genetic variation might contribute to different rehabilitation trajectories.
However, a plausible mechanism does not by itself establish a clinically useful genetic effect.

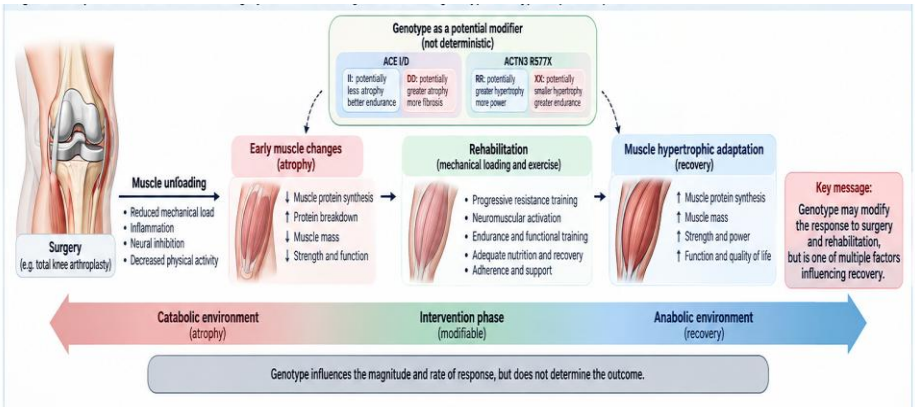


Figure 2. Proposed interaction between surgery, muscle unloading, rehabilitation, genotype and hypertrophic adaptation. Surgery and associated reductions in mechanical loading may contribute to skeletal muscle atrophy and functional decline. Progressive rehabilitation provides a mechanical stimulus for restoration of muscle mass and function. ACE I/D and

ACTN3 R577X polymorphisms may contribute to inter-individual variation in muscle phenotype and adaptation to exercise; however, their influence on postoperative recovery remains insufficiently established. Genetic factors should therefore be interpreted alongside clinical, nutritional, behavioural and rehabilitation-related determinants.

3. ACE I/D Polymorphism and Skeletal Muscle

3.1 Biological characteristics

The ACE gene encodes angiotensin-converting enzyme, a key component of the renin–angiotensin system. The commonly studied I/D polymorphism is associated with differences in ACE activity. The D allele has generally been associated with higher ACE activity, whereas the I allele has been associated with lower activity.

Because the renin–angiotensin system influences vascular regulation, blood flow and other physiological processes relevant to exercise, ACE has been investigated extensively as a candidate gene for physical performance.

Table 1. Biological characteristics of ACE I/D and ACTN3 R577X

Gene	Polymorphism	Main biological feature	Potential relevance
ACE	I/D	Differences in ACE activity	Vascular/exercise physiology
ACTN3	R577X	Presence/absence of α-actinin-3	Fast-fibre contractile function

A 2024 systematic review and meta-analysis examining ACE I/D across sporting modalities found an association between the II genotype and elite endurance performance in several athletic groups. However, the authors also emphasised the specificity of the associations to particular sporting populations and modalities rather than presenting ACE genotype as a universal determinant of performance (Sommers et al., 2024).

This distinction is essential when considering rehabilitation. Postoperative recovery involves substantially different physiological demands from elite endurance or power sport. Consequently, an association between ACE genotype and athletic phenotype should be interpreted as indirect evidence rather than direct evidence of an effect on postoperative recovery.

3.2 ACE genotype and muscle hypertrophy

Evidence relating ACE genotype specifically to muscle hypertrophy is inconsistent.

Charbonneau et al. (2008) examined older men and women before and after 10 weeks of unilateral knee-extensor strength training. ACE genotype was associated with baseline quadriceps muscle volume, with DD carriers showing greater muscle volume than II carriers. However, ACE genotype was not associated with the change in muscle volume or strength produced by the training programme.

This finding is important because it separates a genotype-associated baseline phenotype from a genotype-dependent training response. A person may begin with a different muscle phenotype without necessarily responding differently to resistance training.

A large resistance-training study by Pescatello et al. (2006) similarly found relatively small genotype-related effects. Although some measures of strength response differed between genotype groups, changes in muscle cross-sectional area were not consistently dependent on ACE genotype. The authors concluded that ACE genotype explained only a small proportion of the observed variation in training responses.

Together, these findings suggest that ACE I/D may be associated with certain baseline characteristics or specific aspects of exercise response, but the evidence is insufficient to regard it as a reliable predictor of hypertrophic adaptation.

4. ACTN3 R577X and Skeletal Muscle

4.1 Biological significance of ACTN3

ACTN3 is one of the most extensively investigated genes in sports and exercise science. It encodes α-actinin-3, a structural protein predominantly expressed in fast, type II skeletal muscle fibres.

The R577X polymorphism introduces a premature stop codon. Individuals carrying two X alleles therefore lack functional α-actinin-3, producing the XX genotype. RR individuals express α-actinin-3 normally, while RX individuals express the protein but may exhibit intermediate characteristics.

The biological importance of this polymorphism is supported by experimental and human research. Studies using ACTN3-deficient animal models have demonstrated changes in fast-fibre characteristics, including altered muscle metabolism, contractile properties and fatigue resistance. These observations have provided a potential mechanistic explanation for associations between ACTN3 and human physical performance.

The absence of α-actinin-3 does not represent a disease state. Rather, skeletal muscle appears to compensate for its absence by modifying the expression and functional characteristics of other proteins, including α-actinin-2. This produces a shift toward a more oxidative muscle phenotype (Mills et al., 2001; MacArthur et al., 2008).

5. ACTN3 and Muscle Strength

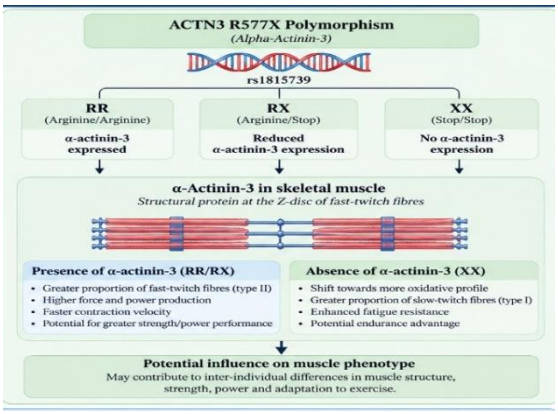
Evidence linking ACTN3 to muscle strength has become stronger in recent years, although the relationship remains outcome-specific.

A 2026 systematic review and meta-analysis included 53 studies examining ACTN3 R577X and different measures of muscle function. Significant associations were identified for one-repetition maximum, maximal voluntary contraction and jumping performance, with the RR, RX and XX genotypes showing different patterns across these outcomes. However, no significant association was identified for several other measures of muscle function (Kamiya-Saito et al., 2026).

This is an important development because it provides a larger evidence base than many earlier individual studies. Nevertheless, the findings do not indicate that ACTN3 determines functional capacity. Rather, they suggest that the variant may contribute modestly to particular aspects of muscle performance.

Earlier work provides a similarly complex picture. Clarkson et al. (2005) examined ACTN3 genotype in men and women participating in a standardised resistance-training programme. Among women, XX homozygotes had lower baseline maximal voluntary contraction but subsequently demonstrated greater gains in one-repetition maximum than RR homozygotes. The genotype explained only a small proportion of the variation in strength adaptation.

These apparently contrasting findings reinforce a broader point: genotype effects may depend on sex, outcome measure, training programme, population and baseline characteristics.



6. ACTN3 and Muscle Hypertrophy

The potential relationship between ACTN3 and muscle hypertrophy is particularly relevant to postoperative rehabilitation. One resistance-training investigation involving 141 men found that ACTN3 genotype was not associated with baseline strength or strength response. However, only R-allele carriers demonstrated increases in muscle thickness following the training programme (Vincent et al., 2012/2013).

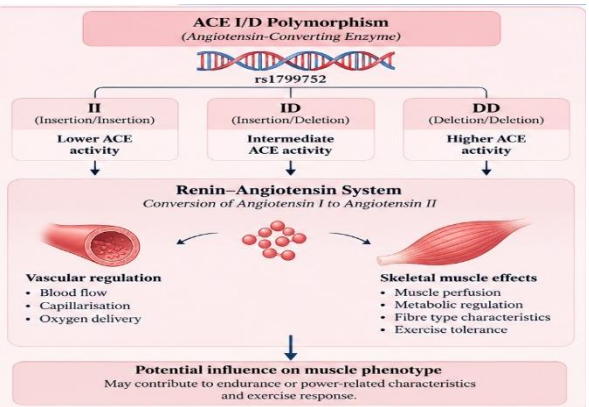
Conversely, Erskine et al. (2014) reported that ACTN3 R-allele carriers had greater quadriceps muscle volume, one-repetition maximum and maximal power at baseline than XX individuals, but the response to nine weeks of knee-extension resistance training was not dependent on ACTN3 genotype.

These studies illustrate why it would be inappropriate to describe ACTN3 as a simple "hypertrophy gene." ACTN3 may influence the starting phenotype of skeletal muscle, yet the extent to which it influences adaptation to resistance training remains uncertain.

Table 2. Evidence linking ACE and ACTN3 with resistance-training adaptation

Study	Gene	Participants	Intervention	Main finding
Pescatello et al. (2006)	ACE	631	12-week RT	Limited genotype-related effects
Charbonneau et al. (2008)	ACE	225	10-week RT	Baseline muscle-volume differences; no hypertrophic genotype effect
Clarkson et al.	ACTN3	602	12-week RT	Sex-specific differences in strength adaptation
Erskine et al. (2014)	ACE + ACTN3	51	9-week RT	ACTN3 related to baseline phenotype; training response largely independent
Recent meta-analysis (2026)	ACTN3	53 studies	Various	Association with selected strength/power outcomes

For postoperative rehabilitation, this distinction becomes even more important. A patient with the XX genotype should not be assumed to have poor hypertrophic potential, nor should an RR carrier automatically be expected to recover faster. The rehabilitation stimulus, nutritional environment and clinical condition remain substantially more important determinants of outcome.



7. ACTN3 and Exercise-Induced Muscle Damage

Muscle damage represents another possible mechanism through which ACTN3 could theoretically influence recovery.

Because α-actinin-3 is located at the Z-disc of fast muscle fibres, its absence could plausibly affect sarcomeric stability during high-force or eccentric contractions. Experimental work in ACTN3-deficient mice has provided some support for this possibility, demonstrating greater force deficits following eccentric contraction under certain loading conditions (Chan et al., 2011).

However, evidence from human exercise studies is considerably less straightforward.

A 2025 systematic review examined ACTN3 R577X and muscle damage following aerobic and strength exercise. Ten studies involving 411 participants were included. Four of the five studies involving strength exercise found no significant genotype-related difference in markers of muscle damage. In contrast, several studies involving prolonged and strenuous endurance exercise reported greater elevations of creatine kinase, myoglobin or lactate dehydrogenase among individuals carrying the X allele (de S e Silva et al., 2025).

The distinction between endurance and resistance exercise is highly relevant to rehabilitation.

Postoperative resistance exercise generally involves carefully controlled and progressively increased mechanical loading rather than the prolonged, high-volume eccentric stress encountered during ultra-endurance activity. Therefore, evidence suggesting increased muscle-damage susceptibility during prolonged endurance exercise should not automatically be applied to postoperative resistance rehabilitation.

At present, there is insufficient evidence to recommend different rehabilitation loading strategies solely according to ACTN3 genotype.

8. Combined Influence of ACE and ACTN3

The possibility that multiple genetic variants may interact is more biologically realistic than expecting a single polymorphism to explain recovery.

ACE and ACTN3 influence different aspects of muscle biology. ACE is associated with vascular and physiological processes, whereas ACTN3 has a direct structural role in fast skeletal muscle fibres.

Erskine et al. (2014) examined the individual and combined influence of both polymorphisms in previously untrained young men undergoing nine weeks of knee-extension resistance training. ACTN3 R-allele carriers demonstrated greater baseline muscle volume, one-repetition maximum and maximal power than XX homozygotes. ACE genotype alone was not associated with muscle phenotypes before or after training. Interestingly, participants with a combination considered "optimal" for muscle performance had greater baseline one-repetition maximum and power than those with a "suboptimal" combination. Nevertheless, training adaptations themselves were not consistently genotype-dependent.

This finding provides an important conceptual basis for postoperative research.

The relevant model may not be:

Genotype → recovery

but rather:

Genotype + clinical condition + rehabilitation stimulus + nutrition + behaviour → recovery

Such a model is much more consistent with the current understanding of exercise genetics

9. ACE and ACTN3 in the Context of Postoperative Rehabilitation

The direct evidence connecting ACE or ACTN3 to postoperative recovery is currently limited. Most available genetic studies have been conducted in healthy adults, athletes or individuals participating in resistance-training programmes.

In contrast, postoperative rehabilitation occurs under a unique combination of biological constraints:

- tissue healing;
- inflammation;
- pain;
- reduced mechanical loading;
- muscle inhibition;
- altered physical activity;
- nutritional challenges;
- progressive restoration of movement;
- gradual increases in exercise intensity.

Consequently, the response to rehabilitation is likely to be influenced by many variables simultaneously.
This does not make genetic research irrelevant. On the contrary, the postoperative environment may provide an informative model for studying genotype-by-training interactions because the rehabilitation stimulus can be more tightly controlled than habitual physical activity.
For example, if patients undergoing the same surgical procedure receive standardised rehabilitation and their ACE and ACTN3 genotypes are known, researchers could examine whether genotype modifies the rate at which muscle mass and strength are regained.
Such a study would be considerably more informative than a simple cross-sectional comparison of genotype frequencies.

10. Proposed Mechanistic Model
The available evidence supports a conceptual rather than causal model.
ACE I/D
↓
ACE activity and related physiological characteristics
ACTN3 R577X
↓
α-actinin-3 expression
fast-fibre characteristics
contractile properties
↓
Interaction with postoperative environment
Surgery
↓
inflammation + pain + unloading
↓
muscle loss and neuromuscular inhibition
↓
Progressive rehabilitation
Mechanical loading
resistance exercise
adequate nutrition
recovery
↓
Muscle adaptation
Muscle protein synthesis
Neuromuscular adaptation
Muscle hypertrophy
Strength restoration
↓
Functional recovery
Mobility
Activities of daily living
Return to work/sport
Quality of life
The important feature of this model is that genotype is positioned as one possible modifier among multiple determinants, rather than as the primary cause of recovery differences.

11. Role of Resistance Exercise in Recovery
The importance of resistance exercise should not be overshadowed by genetic considerations.
The central physiological stimulus for restoring muscle mass is progressive mechanical loading. Resistance exercise stimulates muscle protein synthesis, and repeated exposure to an appropriate training stimulus contributes to hypertrophy over time (Witard et al., 2015).
This principle is supported by rehabilitation research. A systematic review of resistance training in musculoskeletal rehabilitation reported improvements in strength and functional ability across several clinical populations, including patients recovering from joint replacement and ACL reconstruction (Kristensen & Franklyn-Miller, 2012).
More recent evidence following total knee arthroplasty suggests that rehabilitation incorporating progressive resistance exercise can produce greater improvements in muscle mass and strength than standard rehabilitation alone (Monsegue et al., 2024).
Thus, even if ACE or ACTN3 modifies an individual's response, the genetic effect is likely to operate within the broader physiological response to mechanical loading.

12. Nutrition as a Modifier of Muscle Recovery
Nutritional status represents another important factor that should be considered alongside genotype.

Skeletal muscle adaptation depends not only on mechanical stimulation but also on adequate availability of amino acids and energy. Resistance exercise and protein intake can act synergistically to stimulate muscle protein synthesis (Witard et al., 2015).
This is particularly relevant following surgery, when appetite, food intake and metabolic demands may be altered.
A systematic review of protein supplementation following orthopaedic surgery identified beneficial effects on postoperative muscle atrophy and functional outcomes across ACL reconstruction, total hip arthroplasty, total knee arthroplasty and hip-fracture surgery (2024).
Future studies investigating genotype and rehabilitation should therefore measure nutritional intake rather than treating genetics as an isolated explanation for differences in muscle recovery.

13. Clinical Implications
The prospect of personalized rehabilitation based on genetic information is appealing. In theory, patients who are predicted to respond differently to a given exercise stimulus could receive individualized rehabilitation programmes.
However, the current evidence does not support routine ACE or ACTN3 genotyping for postoperative rehabilitation.
There are several reasons.
First, the observed genetic effects are generally modest.
Second, findings vary considerably among studies and populations.
Third, most studies have investigated healthy participants rather than postoperative patients.
Fourth, rehabilitation outcomes are influenced by numerous environmental and clinical variables.
Finally, recent evidence indicates substantial heterogeneity and limited practical significance in genetic associations with athletic performance (2025).
Therefore, genotype should not currently be used to prescribe rehabilitation intensity, determine prognosis or restrict exercise.
The more appropriate clinical position is that ACE and ACTN3 represent potential biomarkers of inter-individual variation that warrant further research.

14. Research Gaps
Several questions remain unanswered.

14.1 Do ACE and ACTN3 influence the rate of postoperative muscle recovery?
This is the most fundamental unanswered question. Longitudinal studies beginning before or immediately after surgery are required.

14.2 Do these variants influence muscle hypertrophy after rehabilitation?
Muscle thickness, cross-sectional area and lean mass should be measured objectively rather than relying solely on body weight or circumference.

14.3 Does genotype interact with rehabilitation dose?
Future studies should determine whether genotype modifies the response to different exercise volumes, intensities or frequencies.

14.4 Are there sex-specific effects?
Previous resistance-training studies have produced different findings in men and women, suggesting that sex may modify genotype–phenotype relationships.

14.5 Does ACTN3 influence recovery from postoperative muscle damage?
The current evidence concerning exercise-induced muscle damage is inconsistent, and postoperative populations have rarely been examined.

14.6 What is the contribution of combined genetic profiles?
Rather than examining individual variants in isolation, future research could investigate polygenic models incorporating ACE, ACTN3 and other variants involved in muscle growth, inflammation, connective-tissue remodelling and recovery.

15. Recommended Design for Future Research
A prospective longitudinal study would provide the strongest approach to addressing the research gap.

Table 3. Factors that should be controlled in future postoperative genotype studies

Domain	Variables
Patient	Age, sex, BMI
Surgery	Procedure, severity, complications

Domain	Variables
Muscle	Baseline mass, strength, CSA
Rehabilitation	Frequency, intensity, volume, adherence
Nutrition	Energy and protein intake
Recovery	Sleep, pain, physical activity
Genetics	ACE I/D, ACTN3 R577X and additional variants

Participants
Patients undergoing a standardised orthopaedic procedure, such as:
anterior cruciate ligament reconstruction;
total knee arthroplasty;
total hip arthroplasty; or
another procedure involving predictable postoperative muscle loss.

Genotyping
ACE
- II
- ID
- DD

ACTN3
- RR
- RX
- XX

Assessment schedule

Time point	Major assessments
Preoperative	Muscle size, strength, function, genotype
2 weeks	Muscle loss, pain, function
6 weeks	Strength and muscle morphology
12 weeks	Hypertrophy and functional recovery
24 weeks	Strength, muscle mass and function
12 months	Long-term recovery

Primary outcomes
Muscle morphology
- ultrasound muscle thickness;
- MRI cross-sectional area;
- DXA lean mass.

Muscle function
- maximal voluntary contraction;
- one-repetition maximum;
- isokinetic strength;
- rate of force development.

Functional recovery
- walking speed;
- stair-climbing ability;
- sit-to-stand performance;
- validated patient-reported outcome measures.

Table 4. Proposed outcomes for future studies

Outcome	Preferred Measurement
Muscle mass	MRI / ultrasound / DXA
Strength	1RM / MVC / isokinetic dynamometry
Muscle damage	CK, myoglobin, LDH
Function	Walking, stair-climb, sit-to-stand
Patient recovery	Validated patient-reported outcomes
Rehabilitation response	Longitudinal change from baseline

Important covariates

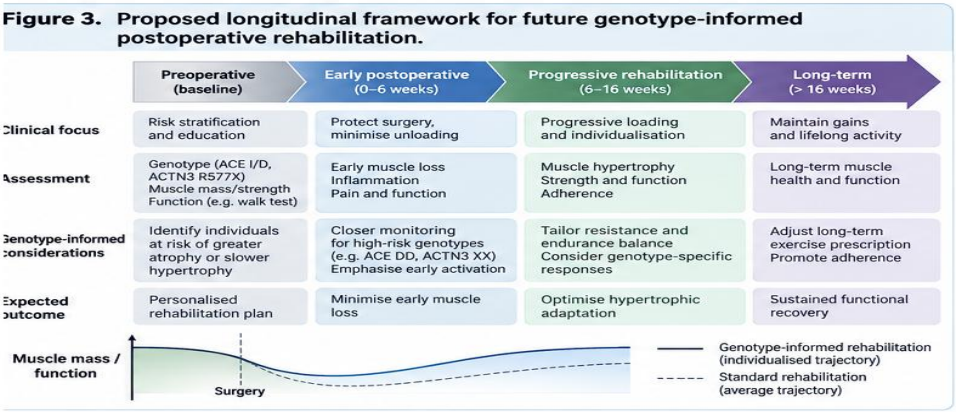
The following variables should be incorporated into statistical models:

- age; baseline muscle mass; baseline strength; surgical procedure; surgical complications; rehabilitation adherence; sex; BMI; exercise volume; nutritional intake; protein intake; physical activity; sleep; smoking/alcohol status where appropriate.

A mixed-effects model could examine whether genotype modifies the trajectory of recovery:

Outcome = time + ACE genotype + ACTN3 genotype + time × ACE + time × ACTN3 + covariates + participant-level random effects

This approach would allow researchers to distinguish baseline genotype-related differences from genuine genotype-dependent changes during
rehabilitation.



16. Limitations of the Existing Literature

The major limitation of the current literature is the scarcity of direct evidence from postoperative populations.

Most ACE and ACTN3 research has been conducted in healthy individuals or athletes. Athletic performance and postoperative recovery represent different biological situations, and findings from one cannot automatically be extrapolated to the other.

A second limitation is the relatively small contribution of individual polymorphisms to complex traits. Muscle strength, hypertrophy and recovery are polygenic and are strongly affected by environmental exposure.

A third limitation concerns differences between studies in training programmes, participant characteristics, outcome measurements and genotype distributions. These methodological differences may contribute to conflicting results.

A fourth limitation is publication bias. Recent evidence suggests that small genetic studies, particularly those examining athletic performance, may be more likely to produce positive findings, emphasising the need for larger and better-controlled studies (2025).

Finally, genetic association should not be confused with causation. Even when a genotype is statistically associated with an outcome, the variant may be linked to another biological pathway rather than directly causing the observed phenotype.

17. Future Directions: From Genetic Association to Precision Rehabilitation

The future of exercise genetics is unlikely to involve a single “optimal” genotype.

Instead, precision rehabilitation may eventually combine genetic information with clinical and behavioural characteristics.

A future rehabilitation model could integrate:

Genetic Profile
Baseline Muscle Phenotype
Surgical Characteristics
Rehabilitation Exposure
Nutritional Status
Functional Response
↓
Individualised Rehabilitation Programme

Such an approach would be more scientifically defensible than attempting to prescribe treatment according to a single polymorphism.

For example, an ACTN3 genotype might eventually contribute to a predictive model alongside age, sex, baseline muscle cross-sectional area and early strength recovery. The value of the genotype would then be judged according to whether it improves prediction beyond conventional clinical variables.

This is the appropriate standard for translating exercise genetics into clinical practice.

18. CONCLUSION

ACE I/D and ACTN3 R577X are biologically plausible candidates for explaining some of the variation observed in skeletal muscle characteristics and responses to exercise. ACTN3 has a particularly direct relationship with fast skeletal muscle fibres, and recent meta-analytic evidence supports associations with selected measures of muscle strength and power. ACE I/D has also been associated with aspects of physical performance and, in some studies, baseline muscle characteristics.

Nevertheless, the evidence does not support the view that either polymorphism independently determines muscle hypertrophy or recovery following surgery. Studies of resistance training have produced inconsistent genotype-related effects, and the direct evidence from postoperative populations remains very limited.

The most defensible interpretation is therefore that ACE and ACTN3 may act as modest biological modifiers within a much larger network of factors governing postoperative muscle recovery. Rehabilitation dose, mechanical loading, nutrition, baseline muscle status, age, sex, surgical factors and adherence are likely to remain considerably more important determinants of outcome.

Future prospective studies should move beyond cross-sectional genotype comparisons and examine whether ACE and ACTN3 modify the longitudinal response to standardised rehabilitation. If such studies demonstrate clinically meaningful effects, genetic information could eventually become one component of precision rehabilitation. At present, however, ACE and ACTN3 genotyping should be regarded as a promising research avenue rather than a routine basis for clinical decision-making.

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Conflict of Interest

The author declares no conflict of interest.

Ethical Approval

Not applicable because this manuscript is a narrative review of previously published literature and does not involve new human or animal data.

Data Availability

No original datasets were generated or analysed for this review.

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