Strength, Hypertrophy & Power Training

Genetic Pathway Reference

9 Functional Categories • ~100 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of skeletal muscle adaptation to resistance, hypertrophy, and power training; the genes that regulate each node of the pathway; the well-studied common variants in those genes; the cofactors each enzyme or signaling component depends on; and the supplement, dietary, and pharmacologic targets that map to each cofactor and pathway. It is intended for clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on published GWAS literature, peer-reviewed mechanistic studies, and meta-analyses through 2025 (sources include J Physiol, J Appl Physiol, Sports Med, Sports Med Open, Nat Genet, Am J Hum Genet, BMC Genomics, FASEB J, Cell Metab, NEJM, and PLoS One). The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations. Most common variants catalogued here confer small individual effects (per-allele odds ratios 1.1–1.5); clinical significance arises from cumulative patterns and gene–pharmacology interactions. A small number of variants — notably ACTN3 R577X (rs1815739), ACVR1B rs2854464, IL15RA rs2228059, MSTN rs1805086, ACE I/D, AR (CAG)n, and rare loss-of-function in MSTN, MYH7, and TTN — have larger or clinically actionable effect sizes.

Heritability of muscle strength phenotypes is substantial. Twin studies estimate heritability at 56–66% for grip strength, knee extension, and elbow flexion (Silventoinen et al., Eur J Hum Genet 2008, n=1,757 twin pairs); 50–80% for lean body mass (Seeman et al., 1996; Arden & Spector, 1997); and ~45% for muscle fiber-type proportion (Simoneau & Bouchard, FASEB J 1995). Heritability of training response is independent: identical-twin studies (HERITAGE Family Study, Bouchard et al., J Appl Physiol 1999; Davidsen et al., J Appl Physiol 2011) find 6–9-fold lower variance within MZ pairs than between unrelated subjects, with ~15% of subjects classified as non-responders and ~15% as high-responders to standardized programs.

2. Pathway Biology

2.1 The hierarchical control of skeletal muscle adaptation

Skeletal muscle is the largest endocrine and metabolic organ in the body and the principal site at which mechanical loading is transduced into structural change. Its adaptation to resistance, hypertrophy, and power training is governed by a hierarchical control system with six logical tiers: (1) anabolic hormone and growth-factor input; (2) the myostatin/TGF-β anabolic brake; (3) sarcomere structure and fiber-type architecture; (4) translational machinery and ribosome biogenesis; (5) the satellite-cell / myogenic regulator pool; and (6) a peripheral layer of vascular, neural, and connective-tissue support. Output force is the integrated product of all six layers — anabolic input minus brake, gated by translational and satellite-cell capacity, expressed through the sarcomere structure, supported by perfusion, neural drive, and tendon force-transmission.

2.2 Tier 1 — Anabolic input: testosterone, IGF-1, mTORC1

Testosterone is the dominant systemic anabolic hormone for skeletal muscle. It binds the androgen receptor (AR), a nuclear hormone receptor whose transactivation domain contains a polymorphic CAG trinucleotide repeat in exon 1 (typically 9–36 repeats; mean ~21 in European populations). Within muscle, longer CAG repeats associate with greater fat-free mass and strength in trained populations, the opposite direction from prostate tissue, where shorter repeats are more transcriptionally active (Ferrando et al., Am J Physiol Endocrinol Metab 2011 in C2C12 myocytes; Guilherme et al., Ann Hum Biol 2021 in bodybuilders n=300). The mechanism for the muscle-specific direction reversal is incompletely understood but may involve coactivator recruitment differences.

IGF-1 / IGF1R signaling activates the PI3K → AKT → TSC2 → Rheb → mTORC1 axis, the central anabolic kinase complex. mTORC1 phosphorylates ribosomal protein S6 kinase 1 (S6K1, encoded by RPS6KB1) and 4E-BP1 (EIF4EBP1) to drive cap-dependent translation initiation. Resistance contractions activate mTORC1 within minutes through both growth-factor-dependent (insulin/IGF-1) and growth-factor-independent (mechanical, phosphatidic acid) pathways. The contraction-induced rise in muscle protein synthesis is approximately 40% within 1–2 hours of acute high-intensity resistance exercise in young humans (Drummond et al., J Physiol 2009). Genetic variation across IGF1, IGF1R, IRS1, AKT1, MTOR, RPS6KB1, EIF4EBP1, and FOXO3 is comprehensively reviewed in companion IGF-1 and Rapamycin/mTOR pathway references; this document focuses on strength-specific extensions and cross-talks.

2.3 Tier 2 — Myostatin / TGF-β anabolic brake

Myostatin (MSTN, also known as growth and differentiation factor 8, GDF-8) is a secreted member of the TGF-β superfamily produced principally by skeletal muscle. It binds the activin type-IIB receptor (ACVR2B, with contributions from ACVR2A), which recruits the type-I receptor ALK4 (ACVR1B) or ALK5 (TGFBR1) to phosphorylate intracellular SMAD2/SMAD3. Activated SMAD2/3 form a complex with SMAD4 and translocate to the nucleus to suppress muscle differentiation genes (MyoD, myogenin) and activate atrophy genes (MuRF1, atrogin-1) via FOXO. The net effect is to brake muscle anabolism.

Loss-of-function mutations in MSTN cause double-muscling phenotypes in cattle, sheep, dogs (Schuelke et al., NEJM 2004 first human case in a German child with biallelic splice-site mutation). Common variants in MSTN (rs1805086 K153R, rs180108 A55T, rs11333758 indel), in the receptors (ACVR1B rs2854464, rs10783485; ACVR2A rs3764955; ACVR2B rs2276541), and in the antagonist follistatin (FST rs3797296) all modulate hypertrophic capacity in normal humans but with smaller effect sizes than the rare loss-of-function. The most-replicated common-variant finding is ACVR1B rs2854464: the G allele is overrepresented in team and power athletes (62% vs 52% controls; Windelinckx et al., 2011) and contributes 2.0–3.6% to limb girth variance.

2.4 Tier 3 — Sarcomere structure and fiber-type architecture

The contractile output of skeletal muscle depends on sarcomere structure (myosin heavy-chain isoform, Z-line scaffold, titin elasticity) and on fiber-type proportion (type I slow-oxidative, type IIa fast-oxidative-glycolytic, type IIx fast-glycolytic). Fiber-type proportion is fixed early in life and only modestly modifiable by training — chronic resistance training shifts type IIx → IIa but does not convert type I → type II in adult humans.

ACTN3 (α-actinin-3) is expressed almost exclusively in fast-twitch (type IIa/IIx) fibers as a Z-line scaffolding protein. The R577X polymorphism (rs1815739, C>T) introduces a premature stop codon — XX homozygotes (~18% global frequency, 16–22% in Europeans) lack α-actinin-3 entirely and show a metabolic shift toward oxidative fast-fiber phenotype. RR is overrepresented in elite power/sprint athletes across multiple cohorts (Yang et al., Am J Hum Genet 2003; Eynon et al., Sports Med 2013; meta-analyses 2019, 2024). The R-allele explains roughly 0.92% of sprint-time variance in elite Caucasian sprinters (Papadimitriou et al., BMC Genomics 2016, n=346 elite sprinters) — small but the difference between qualifying for an Olympic final and not.

MYH7 (β-myosin heavy chain, slow type I), MYH2 (type IIa), MYH1/MYH4 (type IIx), TTN (titin), NEB (nebulin), and MYBPC3 (cardiac myosin-binding protein C) round out the sarcomere genes. Rare missense variants in these genes cause myopathies and cardiomyopathies; common variants confer small effects on strength and athletic capacity.

2.5 Tier 4 — Translational machinery and ribosome biogenesis

mTORC1 activation initiates protein synthesis through phosphorylation of S6K1 and 4E-BP1, but the chronic hypertrophic response is increasingly understood to be limited by ribosome content (translational capacity) rather than acute signaling intensity. High-responders to resistance training show dramatically larger increases in total RNA per mg muscle (a proxy for ribosome content) than low-responders (Hammarström et al., J Physiol 2020 within-participant single-vs-multiple-set design; Figueiredo et al., AJP-Endo 2021 review). Ribosome biogenesis is driven synergistically by mTORC1 (through S6K1) and by the transcription factor c-Myc, which activates RNA polymerase I transcription of pre-rRNA. Common variants in MYC, POLR1B (POL I subunit), UBTF (upstream binding transcription factor), RPS6KB1, and EIF4EBP1 are candidate modifiers, though GWAS-grade evidence for these is less developed than for sarcomere and brake genes.

2.6 Tier 5 — Satellite cells and myogenic regulators

Skeletal muscle is a postmitotic tissue: mature fibers do not divide. Hypertrophy beyond a threshold (~30% cross-sectional area increase) requires the addition of new myonuclei, which are donated by satellite cells — quiescent muscle stem cells located between the basal lamina and sarcolemma, marked by PAX7 expression. On activation by injury, mechanical load, or growth factors, satellite cells exit quiescence (PAX7 maintained, MYF5 induced), proliferate (MYOD1), differentiate (myogenin/MYOG), and fuse to existing fibers, donating their nuclei. High-responders to resistance training show substantially larger satellite-cell pools at baseline and dramatically larger satellite-cell expansion with training (Petrella et al., J Appl Physiol 2008; Bamman et al., 2007 — extreme-, modest-, and non-responder classification by Δ vastus lateralis fiber CSA).

IL-15 is an anabolic myokine secreted by skeletal muscle that signals through the heterotrimeric IL-15 receptor (IL15RA, IL2RB, common γ chain). The IL15RA exon 7 polymorphism rs2228059 (1775 A>C) accounts for ~7.1% of variation in muscle hypertrophy response to 10-week resistance training in young men and women, and an exon 4 variant adds ~3.5% (Riechman et al., J Appl Physiol 2004 MERET cohort, n=153; Pistilli et al., 2008 FAMuSS). Additional GWAS-implicated strength modifiers include LRPPRC rs10186876, MMS22L rs9320823, ARK2N tag SNPs, and PHACTR1 rs6905419 (Ahmetov et al. reviews 2016, 2022). NTRK2 (TrkB receptor for BDNF) variants modulate satellite cell function and motor recovery after rehabilitation.

2.7 Tier 6 — Substrate, energy buffer, and power

Power output (force × velocity) for efforts of <30 seconds is dominated by the phosphagen (creatine phosphate, PCr) system and anaerobic glycolysis. Muscle creatine kinase (CKM) catalyzes the rapid transfer of high-energy phosphate from phosphocreatine to ADP, regenerating ATP at the contractile apparatus. AMP deaminase (AMPD1) converts AMP to IMP during high-intensity exercise, preventing AMP accumulation that would inhibit ATP regeneration; the rs17602729 (Q12X) nonsense variant causes muscle AMPD1 deficiency in TT homozygotes, who are essentially absent from elite athletic populations (CC overrepresented OR ~1.7 vs controls; El Ouali et al., Sports Med Open 2025, n=5,717). Glycogen storage capacity, set in part by PPP1R3A (Savage et al., PLoS Med 2008), determines glycolytic substrate availability for repeated high-intensity efforts.

2.8 Tier 7 — Vascular delivery, sympathetic input, and the renin-angiotensin axis

Power and strength performance depend on rapid muscle perfusion and sympathetic activation. ACE (angiotensin-converting enzyme) catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II. The ACE I/D polymorphism (rs1799752, 287-bp Alu insertion in intron 16) determines tissue and circulating ACE activity: II carriers have ~50% the ACE activity of DD carriers, with ID intermediate. The D allele (higher ACE activity, more angiotensin II, greater muscle hypertrophy response in some training studies) is overrepresented in sprinters and weightlifters; the I allele (lower activity, better cardiovascular efficiency) is overrepresented in endurance athletes. DD sprinters showed faster 400m times than II in the Papadimitriou multi-cohort study (46.94 vs 48.50 sec, p=0.003). Note: the ACE I/D Alu indel is not directly callable from short-read SNP-only VCF data and must be inferred from rs4341/rs4342/rs4343 tag SNPs in tight LD.

AGT (angiotensinogen) rs699 (M235T) and AGTR2 (angiotensin II receptor type 2) rs11091046 modify the same axis. NOS3 (endothelial NOS) rs2070744 and rs1799983 affect basal nitric oxide tone and exercise-induced vasodilation (covered in greater depth in the Endothelial pathway reference).

2.9 Tier 8 — Neural drive and motor learning

Strength gains in the first 2–4 weeks of training are dominated by neural adaptations — improved motor unit recruitment, synchronization, and rate coding — rather than hypertrophy. Brain-derived neurotrophic factor (BDNF) modulates activity-dependent synaptic plasticity. The Val66Met polymorphism (rs6265, G>A) impairs activity-dependent BDNF secretion in Met carriers; Val/Val homozygotes show better motor learning, larger hippocampal volumes, and greater acute exercise-induced BDNF response in most studies (Egan et al., Cell 2003; Kleim et al., Nat Neurosci 2006; meta-analyses 2017, 2020). Met carriers represent ~25–30% of European populations.

Dopaminergic tone modulates motivation, neural drive, and reinforcement of motor patterns. DRD2 / ANKK1 rs1800497 (Taq1A, glu713lys) Lys carriers have reduced striatal D2 receptor density; Glu/Glu showed enhanced motor learning after acute aerobic exercise in interaction analyses (Mang et al., Sci Rep 2017). COMT rs4680 (Val158Met) Val/Val faster prefrontal dopamine clearance; the so-called warrior phenotype, generally favorable for high-arousal performance under stress.

2.10 Tier 9 — Connective tissue, tendon, and recovery

Force generated by sarcomeres is transmitted through tendons to bone. Type I collagen is the primary tendon protein. COL1A1 rs1800012 (G>T at the Sp1 transcription factor binding site in intron 1) reduces Sp1 binding affinity in T carriers, altering the α1:α2 collagen ratio; the rare TT genotype is protective against tendon and ligament injuries (meta-analysis OR 0.21 vs GT/GG, p<0.001; Wang et al., Oncotarget 2017, n=2,314). However, COL1A1 T-allele carriers are paradoxically weaker pre- and post-eccentric muscle damage (Lulińska-Kuklik et al., Eur J Appl Physiol 2018), illustrating that injury-protective and strength-favoring directions can dissociate.

COL5A1 rs12722 (3' UTR T>C) modulates type V collagen, a regulator of type I fibril assembly. TT is associated with reduced flexibility, weaker tendon fiber assembly, and increased Achilles tendinopathy risk in multiple meta-analyses; the C allele is protective for tendon injury. MMP3 rs679620 modulates tendon collagen turnover; IL6 rs1800795 modifies acute exercise-induced inflammation (covered in Inflammation report); VEGFA rs2010963 affects training-induced capillary density. VDR (vitamin D receptor) FokI (rs2228570), BsmI (rs1544410), TaqI (rs731236), ApaI (rs7975232), and Cdx2 (rs11568820) variants modulate skeletal muscle vitamin D signaling and have been associated with sarcopenia risk and muscle strength in older populations, with mixed direction across cohorts.

2.11 Pharmacology integration: rapamycin and resistance training

Rapamycin (sirolimus) binds the immunophilin FKBP12 (FKBP1A); the FKBP12-rapamycin complex docks onto the FRB domain of mTOR within mTORC1 and allosterically inhibits kinase activity. Acute oral rapamycin (16 mg) administered 1–2 hours before high-intensity resistance exercise in young men completely blocked the contraction-induced ~40% rise in muscle protein synthesis (Drummond et al., J Physiol 2009, n=14), while the same dose did not affect basal post-absorptive muscle protein metabolism (Dickinson et al., 2012). Rodent chronic-loading studies show that rapamycin-sensitive mTOR partially mediates ribosome biogenesis and hypertrophy in response to repeated resistance contractions, but does not fully account for the chronic adaptation — rapamycin-insensitive pathways (ERK/MNK1, mTORC2 in chronic dosing, c-Myc-driven rRNA synthesis, satellite-cell-mediated myonuclear addition) carry meaningful load on long timescales (Ogasawara et al., Sci Rep 2016; Goodman et al., Sports Med 2014 review).

In bi-weekly pulsed dosing protocols typical of longevity practice, sirolimus whole-blood levels peak at 30–60 ng/mL within 1–3 hours of dose and decline to <2 ng/mL by day 7–10, depending on CYP3A4 and CYP3A5 metabolism. The interference window for contraction-induced muscle protein synthesis is therefore primarily the first 24–48 hours after dose, with progressive recovery over days 3–10.

3. Functional Gene Catalog by Category

3.1 Androgen axis

Genes regulating testosterone synthesis, transport, conversion, and AR-mediated signal transduction. AR sensitivity is the principal genetic lever for muscle anabolism in this category.

Gene	rsID / variant	Functional consequence	Cofactor / node
AR	(CAG)n exon 1	Polyglutamine repeat 9–36; in muscle, longer ≥21 repeats associate with greater fat-free mass and strength in bodybuilders (Guilherme et al., Ann Hum Biol 2021); C2C12 transactivation increases with repeat length (Ferrando et al., Am J Physiol 2011). Note: opposite direction from prostate tissue. Microsatellite NOT directly callable from SNP-only VCF.	Zn^{2+} (zinc finger), HSP90/FKBP4
AR	rs6152	X-linked tag SNP for AR/EDA2R Xq12	Same as

Gene	rsID / variant	Functional consequence	Cofactor / node
	(synonymous E211E)	haplotype; AGA-relevant; Ellis 2007. Muscle direction unresolved.	above
SHBG	rs1799941 (G>A)	A allele higher SHBG, lower free testosterone (Ohlsson et al., PLoS Genet 2011, GWAS).	Hepatic glycoprotein
SHBG	rs6259 (D356N)	N allele increases SHBG levels modestly.	Same
CYP19A1	rs2470152, rs4646	Aromatase; modulates testosterone:estradiol ratio (covered in Hair Loss reference).	heme (Fe), NADPH
CYP17A1	rs743572 (-34 T/C)	Modest 17α-hydroxylase/lyase activity effect; weak strength signal.	heme (Fe), NADPH
SRD5A1, SRD5A2	rs39848, rs248793, rs523349, rs632148	5α-reductase; converts T → DHT. Muscle expresses primarily AR, not DHT-dependent. Covered fully in Hair Loss reference.	NADPH
FKBP4	various	AR cochaperone (FKBP52); modest role in AR transactivation.	Hsp90 chaperone complex

AR (CAG)n is the most consequential variant in this category for muscle phenotype but requires specialized repeat-genotyping (PCR + capillary electrophoresis or long-read sequencing) — it cannot be reliably called from short-read whole-genome sequencing of typical depth. SHBG variants modify the free-testosterone fraction and may be more relevant for men with borderline-low total testosterone.

3.2 GH / IGF-1 / mTORC1 anabolic input — cross-reference

This category is comprehensively covered in the IGF-1 Regulation Genetic Pathway Reference and the Rapamycin / mTOR Genetic Pathway Reference. The genes catalogued there (IGF1, IGF1R, IRS1, IRS2, PIK3CA, AKT1, AKT2, MTOR, RPTOR, RICTOR, TSC1, TSC2, RHEB, PRKAA1, PRKAA2, FKBP1A, RPS6KB1, EIF4EBP1, FOXO1, FOXO3, GH1, GHR, IGFBP3, KLOTHO, PAPPA, PAPPA2) are not re-catalogued here. The strength-relevant interpretation layer — how a given AKT1/MTOR/FOXO3/IRS1 genotype interacts with myostatin braking, satellite-cell capacity, and rapamycin pharmacology — is treated in the convergence analyses of the personalized companion report.

For ease of cross-reference, the strongest replicated variants in this axis with direct strength-training relevance are: IGF1 rs35767 (-1245 C/T), IGF1R rs2229765 (E1043E), IRS1 rs2943641 (insulin sensitivity), AKT1 rs1130214 and rs2494752, MTOR rs2295080 (promoter), FOXO3 longevity haplotype (rs2802292, rs2764264, rs2253310), and GH1 rs2665802 (training-induced strength gains in FAMuSS subset).

3.3 Myostatin / TGF-β anabolic brake

Myostatin is the dominant negative regulator of muscle mass. The brake operates through the activin type-II receptor (ACVR2B with contributions from ACVR2A), the type-I receptor ALK4 (ACVR1B), and SMAD2/3 transcription factors. Common variants modulate the strength of this brake.

Gene	rsID / variant	Functional consequence	Cofactor / node
MSTN	rs1805086 (K153R, A>G)	G (R) allele rare (MAF ~1–4%); R/R essentially absent. K/R associated with greater biceps brachii thickness (Δ 14.7%, $p<0.05$) in elderly women (Stebbings et al., Genes 2020, n=290). Loss-of-function rare variants cause double-muscling (Schuelke NEJM 2004).	secreted ligand
MSTN	rs180108 (A55T, G>A)	T (T55) modulates strength recovery after eccentric muscle damage and training-induced hypertrophy (Kostek 2009).	secreted ligand
MSTN	rs11333758 (-/-indel)	−/− overrepresented in high-elite mixed-sport Polish athletes (Leońska-Duniec et al., BMC Genomics 2023, n=797).	secreted ligand
ACVR1B (ALK4)	rs2854464 (A>G)	G allele overrepresented in team athletes (60.4%) and power athletes (62.0%) vs controls (52.3%); contributes 2.0–3.6% to limb-girth variance (Windelinckx 2011; Kostek 2014). G is the muscle-favoring allele.	type-I receptor kinase, ATP
ACVR1B	rs10783485 (G>T)	T allele carriers: greater biceps brachii thickness (Δ 4.6%) and vastus lateralis ACSA in elderly (Stebbings 2020).	type-I receptor kinase
ACVR2A	rs3764955 (G>C)	CC and GG associated with high-elite athlete status; gene-gene interaction with MSTN rs11333758 (Leońska-Duniec 2023).	type-II receptor
ACVR2B	rs2276541 (T>C)	Associated with lean body mass in older women (Walsh et al., 2007).	type-II receptor
FST	rs3797296	Follistatin (myostatin antagonist); less-replicated candidate.	secreted antagonist
SMAD3	rs7178347	Modest effects on TGF-β signaling output.	transcription factor
GDF11	rare variants	Closely related to MSTN; common variant data sparse.	secreted ligand

ACVR1B rs2854464 is the most-replicated common variant in the brake category, with athlete-status effects across team-sport, power, and endurance cohorts. The G allele consistently associates with muscle-mass-favoring phenotypes. MSTN K153R has a substantial effect when present (Δ 14.7% biceps thickness in heterozygotes) but is rare. Combined-genotype effects across MSTN + ACVR1B + ACVR2A may capture additional variance per Leońska-Duniec 2023 gene-gene interaction analysis.

3.4 Sarcomere structure and fiber-type architecture

Genes encoding the contractile proteins, Z-line scaffolding, and cytoskeletal components that define fiber type and force-generating capacity. Fiber-type proportion is approximately 45% heritable and only modestly modifiable by training.

Gene	rsID / variant	Functional consequence	Cofactor / node
ACTN3	rs1815739 (R577X, C>T)	T (X) introduces premature stop; XX null lacks α-actinin-3 in fast fibers, with metabolic shift toward oxidative phenotype. RR overrepresented in elite power/sprint athletes (OR ~1.3–1.5 vs controls; Yang 2003; Eynon 2013; meta-analyses 2019, 2024). RR Caucasian sprinters faster 200m (21.19 vs 21.86 sec) and 400m (46.94 vs 48.50 sec) than XX (Papadimitriou BMC Genomics 2016, n=346).	Z-line scaffold (fast fibers)
MYH7	rare missense	β-MHC slow type I; rare variants cause hypertrophic cardiomyopathy. Common-variant strength signal weak.	myosin head ATPase
MYH2	rare missense	Type IIa myosin heavy chain; rare variants cause inclusion body myopathy.	myosin head ATPase
MYH1, MYH4	various	Type IIx and embryonic/perinatal myosin; less-studied.	myosin head ATPase
TTN	rs10497520 etc.	Titin; rare variants cause cardiomyopathy/myopathy. rs10497520 has weak grip-strength association.	sarcomere spring
NEB	rare	Nebulin; rare variants cause nemaline myopathy.	thin-filament length regulator
MYBPC3	rs1052373 (V158M)	Cardiac MyBP-C; weak power-associated variant in some panels (Ahmetov 2016 review).	myosin-binding protein C
MYL2, MYL3	various rare	Myosin light chains; HCM-associated rare variants.	myosin regulator
TNNT3, TNNI2	various	Fast-skeletal troponins; less-studied common variants.	Ca^{2+}-regulated contraction

ACTN3 R577X is the single most-studied variant in sports genomics. Its effect is most pronounced at the elite-vs-elite contrast (power athletes vs endurance athletes); the contrast versus non-athlete controls is more modest. RR explains roughly 0.92% of sprint-time variance in elite Caucasians — small in absolute terms but practically meaningful at the international competition margin. Most other sarcomere-gene strength signals are driven by rare myopathy-causing variants rather than common polymorphisms; for hypertrophy and power in normal-population genetics, ACTN3 stands alone in this category.

3.5 Substrate, energy buffer, and power output

Genes governing the phosphagen system, anaerobic glycolysis, glycogen storage, and AMP/IMP cycling — substrate availability for high-intensity efforts of seconds to minutes.

Gene	rsID / variant	Functional consequence	Cofactor / node
CKM	rs8111989 (NcoI A/G, 3'UTR)	Muscle creatine kinase; meta-analyses link polymorphism to VO$_2$max variation (Heled 2007; Fedotovskaya 2014). Direction inconsistent across cohorts.	Mg^{2+}-ATP, creatine

Gene	rsID / variant	Functional consequence	Cofactor / node
CKM	rs1803285	Promoter variant; less-replicated.	Same
AMPD1	rs17602729 (Q12X, C>T)	T (X) allele = nonsense → AMPD1 deficiency. CC overrepresented in athletes OR ~1.7 vs controls; TT essentially absent in athletes (El Ouali 2025, n=5,717). CC is power-favoring.	Zn^{2+}
PPP1R3A	rs112443063 (R905X)	Loss-of-function reduces glycogen storage, potentially limiting glycolytic output (Savage et al., PLoS Med 2008).	PP1 glycogen-targeting subunit
CPNE5	rs3213537	Copine-5; power-associated in Eastern European cohorts (Ahmetov 2016 review).	Ca^{2+}-binding protein
NRF2 (NFE2L2)	rs6721961 (-617 C/A)	A allele lower antioxidant promoter activity (Marzec FASEB J 2007). Indirect effect on training-recovery; covered in Endurance reference.	Keap1-regulated transcription
UCP3	rs1800849	Mitochondrial uncoupling protein 3; modest fiber-type and substrate-utilization effects.	Mitochondrial inner membrane
LDHA, LDHB	various	Lactate dehydrogenase; ratios shift with training but common-variant effects modest.	NAD^+/NADH

AMPD1 rs17602729 is recessive: only TT homozygotes are protein-deficient, and they are essentially absent from athletic populations. Heterozygotes have intermediate enzyme activity but show only modest performance reduction. CC is the expected athlete-favoring genotype across both endurance and power phenotypes. This is one of few power-genetics variants where the homozygous risk genotype is essentially incompatible with elite-level performance.

3.6 Translation initiation and ribosome biogenesis

Genes encoding the protein-synthesis machinery and the transcriptional drivers of ribosomal RNA. Recent evidence (Hammarström J Physiol 2020; Figueiredo AJP-Endo 2021) suggests ribosome content is a stronger predictor of chronic hypertrophic response than acute mTORC1 signaling intensity. GWAS-grade common-variant evidence in this category is less developed than for sarcomere and brake genes.

Gene	rsID / variant	Functional consequence	Cofactor / node
RPS6KB1	rs17158836, rs180515	S6 kinase 1; mTORC1 substrate driving translation initiation and ribosome biogenesis.	ATP, Mg^{2+}
EIF4EBP1	rs1973700	4E-BP1; phosphorylated by mTORC1 to release eIF4E for cap-dependent translation.	Same
EIF4E	rs1051535	Cap-binding factor; rate-limiting for translation initiation.	m^7G cap recognition
MYC	rs6983267	Drives RNA polymerase I transcription of pre-rRNA; cancer-associated variant with potential muscle relevance.	DNA-binding transcription factor

Gene	rsID / variant	Functional consequence	Cofactor / node
POLR1B	tag SNPs	RNA polymerase I subunit; rRNA transcription.	Same
UBTF	tag SNPs	Upstream binding transcription factor; rRNA gene activation.	RNA pol I cofactor
RRM1, RRM2	various	Ribonucleotide reductase; nucleotide supply for rRNA synthesis.	Fe^{2+}, NADPH
TIF1A (RRN3)	tag SNPs	Pol I transcription initiation factor.	Same

This category is biologically central but genetically under-studied. No common variants in this set have GWAS-grade replication for strength or hypertrophy phenotypes as of 2025. The category is included for completeness and because the underlying biology — ribosome biogenesis as the limiting step for chronic hypertrophy — is increasingly well-supported by mechanistic studies. Future GWAS may identify clinically actionable variants here.

3.7 Satellite cells and myogenic regulation

Genes encoding satellite-cell quiescence, activation, proliferation, differentiation, and fusion — the muscle stem-cell pathway responsible for myonuclear addition during hypertrophy beyond ~30% CSA increase.

Gene	rsID / variant	Functional consequence	Cofactor / node
PAX7	rare missense	Master regulator of satellite-cell identity and quiescence; rare LoF causes congenital myopathy.	DNA-binding TF
MYF5	rs806124	Myogenic regulator; SC activation. Common-variant data sparse.	bHLH TF
MYOD1	rs6537486	Master myogenic TF; SC proliferation and differentiation commitment.	bHLH TF
MYOG (myogenin)	rs2070840	Differentiation TF; required for myoblast fusion.	bHLH TF
MEF2C	rs1366594	Cooperates with MyoD/myogenin; hypertrophy-associated locus in some GWAS.	MADS-box TF
NOTCH1	various	SC quiescence maintenance; rare LoF disrupts SC homeostasis.	Cell-surface receptor
NCAM1	rs2229767	Neural cell adhesion molecule; SC-myofiber interaction.	Cell adhesion
CDKN1A (p21)	rs1801270	SC cell-cycle arrest; modulates SC pool dynamics.	CDK inhibitor

Common-variant evidence in the satellite-cell category is weaker than for adjacent categories. The strongest evidence for SC contribution to hypertrophic responsiveness comes from histological studies (Petrella 2008; Bamman 2007) showing high-responders have larger baseline SC pools and greater training-induced SC expansion than low-responders. Whether this is genetically determined (tier 5) or downstream of upstream tiers (anabolic input, IL-15 *signaling) is still being parsed. The IL15RA variants in section 3.8 are the strongest genetic anchor for this pathway in current GWAS.*

3.8 Hypertrophy modifiers and myokine signaling

Genes outside the canonical anabolic input → brake → translation → SC chain that nonetheless modify the magnitude of hypertrophy or strength gain. Includes the IL-15 myokine axis, neurotrophin receptors, and a series of GWAS-implicated strength-associated loci.

Gene	rsID / variant	Functional consequence	Cofactor / node
IL15RA	rs2228059 (1775 A>C, exon 7)	A allele modulates baseline whole-muscle volume/quality; accounts for 7.1% of hypertrophy-response variance to 10wk RT (Riechman J Appl Physiol 2004 MERET, n=153; Pistilli 2008 FAMuSS). AA men spend more time in light-intensity activity than CC.	IL-15 receptor α subunit
IL15RA	exon 4 variant	Independent ~3.5% additional variance in hypertrophy (same studies).	Same
IL15	rs1057972	IL-15 ligand variant; modest effects.	Myokine
NTRK2	rs2289656, rs1212171	TrkB receptor for BDNF; modifies motor recovery after rehabilitation (Mori et al., Front Neurol 2022). Indirect strength effect via neuromuscular plasticity.	Receptor tyrosine kinase
LRPPRC	rs10186876	Strength-associated marker, replicated in two cohorts (Ahmetov 2016 review).	Mitochondrial RNA-binding protein
MMS22L	rs9320823	Strength-associated marker (Ahmetov 2016).	DNA replication/repair
ARK2N (C18orf25)	tag SNPs	Strength-associated marker.	Less characterized
PHACTR1	rs6905419	Strength-associated marker (Gineviciene et al., 2014).	Phosphatase and actin regulator
GH1	rs2665802 (T>A)	Promoter variant; A allele associated with greater RT-induced strength gains in FAMuSS subset.	GH1 expression
LEP	rs7799039 (-2548 G>A)	Leptin promoter; modifies body-composition response to training.	Adipokine
LEPR	rs1137101 (Q223R)	Leptin receptor; satiety and energy expenditure modifier.	Cytokine receptor
FTO	rs9939609 (T>A)	A allele obesity-associated; vastus lateralis ACSA effect in elderly (Stebbings 2020); greater fat loss with intense exercise (Zarebska 2019, n=234).	Obesity-associated locus
PPARG	rs1801282 (Pro12Ala)	C (Ala12) allele associated with greater body-composition response to RT (Zarebska 2017, n=201). Also covered in Lipoprotein/Glucose	Adipocyte differentiation TF

Gene	rsID / variant	Functional consequence	Cofactor / node
		references.	
MTHFR	rs1801133 (C677T)	T allele (677T) reduces enzyme activity; modifies recovery and oxidative stress (covered in Homocysteine reference). Strength-relevant via methylation environment.	FAD, folate

IL15RA rs2228059 is the strongest single-variant predictor of hypertrophy response in well-controlled human resistance-training studies, accounting for ~7% of variance. The MERET and FAMuSS cohorts together (~1,500 subjects) provide the strongest evidence base for any common variant in this category. The remaining markers (LRPPRC, MMS22L, ARK2N, PHACTR1) emerged from multi-cohort strength-associated locus reviews (Ahmetov 2016, 2022) but have less mechanistic characterization.

3.9 Power, neural drive, vascular, and connective tissue

Peripheral support genes for power output, neural drive and motor learning, capillary perfusion, and tendon force transmission. Smaller effect sizes individually but collectively shape the expression of strength as observable phenotype.

Gene	rsID / variant	Functional consequence	Cofactor / node
ACE	rs1799752 (I/D Alu indel)	D allele higher tissue ACE activity; favors power/sprint phenotypes (DD OR ~1.2–1.5 vs II for power; meta-analysis Ma PLoS One 2013, n>10,000). DD sprinters faster 400m than II (46.94 vs 48.50 sec; Papadimitriou 2016). Indel NOT directly callable from SNP-only VCF — inferred from rs4341/rs4342/rs4343 tag SNPs.	Zn^{2+} metallopeptidase
AGT	rs699 (M235T, T>C)	T allele higher angiotensinogen levels; modest power association.	Liver α2-globulin
AGTR2	rs11091046 (X-linked A>C)	C allele in males associated with power-athlete status.	Angiotensin II receptor 2
NOS3	rs2070744 (-786 T>C)	C allele reduced eNOS promoter activity → vasoconstriction. Covered in Endothelial reference.	BH4, arginine, FAD/FMN/NADPH, calmodulin
NOS3	rs1799983 (G894T, E298D)	T (D298) reduced eNOS activity; muscle perfusion effect.	Same
BDNF	rs6265 (Val66Met, G>A)	A (Met) allele impairs activity-dependent BDNF secretion; reduced motor learning (Egan Cell 2003); ~25–30% Met-carrier frequency in Europeans. Val/Val is the favorable allele for skill acquisition.	TrkB receptor signaling
DRD2 / ANKK1	rs1800497 (Taq1A, G>A)	A (Lys713) allele reduced striatal D2 density; Glu/Glu enhanced motor learning after acute exercise (Mang Sci Rep 2017).	Dopamine receptor D2

Gene	rsID / variant	Functional consequence	Cofactor / node
COMT	rs4680 (Val158Met, G>A)	A (Met158) allele slower dopamine clearance; Val/Val (G/G) faster — "warrior" phenotype, favorable for high-arousal performance.	S-adenosylmethionine, Mg^{2+}
COL1A1	rs1800012 (Sp1 site, G>T)	T (rare) reduces Sp1 binding, alters α1:α2 collagen ratio. TT protective for tendon/ligament injury (meta-analysis OR 0.21; Wang Oncotarget 2017). Paradoxically, T-allele carriers were weaker pre/post EIMD (Lulińska-Kuklik Eur J Appl Physiol 2018).	Vit C, Fe, Cu (lysyl oxidase)
COL5A1	rs12722 (3'UTR T>C)	TT associated with reduced flexibility, Achilles tendinopathy risk (multiple meta-analyses). C allele protective for tendon injury.	Vit C, Cu
COL5A1	rs13946 (T>C)	Tag SNP in COL5A1 haplotype; injury risk modifier.	Same
COL3A1	rs1800255 (G>A)	Type III collagen; less-replicated injury association.	Vit C, Cu
MMP3	rs679620 (E45K)	Modulates tendon collagen turnover.	Zn^{2+}
IL6	rs1800795 (-174 G>C)	G allele higher IL-6 production; covered in Inflammation reference. Modifies acute exercise-induced inflammation and recovery.	Cytokine
TNF	rs1800629 (-308 G>A)	A allele higher TNF expression; covered in Inflammation reference.	Cytokine
VEGFA	rs2010963 (-634 G>C)	C allele lower VEGF; affects training-induced capillary density.	Hypoxia-induced angiogenic factor
VDR	rs2228570 (FokI T>C)	C (F) allele truncated VDR isoform, more transcriptionally active; FF/CC associated with sarcopenia risk (Yao J Clin Lab Anal 2020) and lower knee extensor strength in some cohorts. Mixed direction across studies.	1,25-$(OH)_2$-D_3, RXR partner
VDR	rs1544410 (BsmI A>G)	BB (G/G) homozygotes higher knee extensor strength in elderly Turkish men (Bahat Aging Clin Exp Res 2010).	Same
VDR	rs7975232 (ApaI), rs731236 (TaqI), rs11568820 (Cdx2)	Haplotype-defining VDR variants; mixed strength associations across cohorts.	Same

ACE I/D and ACTN3 R577X are the two most-replicated sports-genomics variants and represent the canonical "power axis." Individually, each accounts for ~1–1.5% of elite sprint-time variance — small in absolute terms but the practical difference between national-level and international-level performance. The collagen genes (COL1A1, COL5A1) carry injury-risk *effects of greater clinical magnitude than their direct strength effects. BDNF Val66Met is the strongest single neural-drive variant. VDR variants have mixed evidence across cohorts and are likely modulated by 25(OH)D status.*

4. Cofactor and Intervention Target Map

This table maps each functional category to the cofactors and effectors its genes require, and to the supplement, dietary, or lifestyle interventions that plausibly modulate them. This is a generic catalog of biochemical relationships, not a personalized recommendation.

Category	**Cofactors / effectors**	**Intervention targets**
Androgen axis (AR, SHBG, SRD5A, CYP19A1)	Zinc (AR zinc finger), HSP90 chaperones, NADPH (5α-reductase), heme (aromatase). Cholesterol substrate for steroidogenesis.	Zinc sufficiency; manage SHBG (insulin sensitivity, body composition); pharmacological 5α-reductase inhibition (finasteride/dutasteride) for DHT-target tissues; aromatase inhibitors (medical context only)
GH / IGF-1 / mTORC1 (cross-ref)	ATP, Mg^{2+}, amino acids (especially leucine), insulin, IGF-1. Sleep architecture for GH pulses.	Adequate sleep; protein/leucine timing; resistance training for IGF-1R upregulation; rapamycin for mTORC1 inhibition (longevity context); see IGF-1 and Rapamycin references
Myostatin / TGF-β brake (MSTN, ACVR1B/2A/2B, FST, SMAD)	Secreted ligands; receptor kinases need ATP. Furin proteases for MSTN processing.	Resistance training (most natural anti-myostatin signal — exercise lowers serum and muscle myostatin). Investigational anti-myostatin biologics (bimagrumab, apitegromab — clinical trial only). Follistatin gene therapy (research only).
Sarcomere / fiber type (ACTN3, MYH, TTN, NEB)	Myosin head ATP, Ca^{2+} for thin-filament activation, magnesium for cross-bridge cycling.	No genetic modifier intervention; training shifts IIx → IIa via fiber-type plasticity; magnesium sufficiency
Substrate / energy buffer (CKM, AMPD1, PPP1R3A)	Mg^{2+}-ATP, creatine, phosphocreatine, glycogen, AMP/IMP cycling, Zn^{2+} (AMPD1).	Creatine monohydrate 3–5 g/d (well-evidenced for power and muscle mass); β-alanine 4–6 g/d for buffering; carbohydrate periodization for glycogen
Translation / ribosome biogenesis (RPS6KB1, MYC, POLR1B)	ATP, Mg^{2+}, ribonucleotides, methionine (initiator tRNA).	Adequate protein and energy intake; volume-progressive RT (drives ribosome biogenesis); training periodization for accumulated translational capacity
Satellite cells / myogenic (PAX7, MYF5, MYOD, MYOG, NOTCH)	NAD^+, IGF-1, mechanical stretch, growth factors. NOTCH ligands for quiescence.	Resistance training (primary SC activator); ensure protein/leucine; investigational NAD^+ precursors; avoid chronic glucocorticoids

Category	Cofactors / effectors	Intervention targets
Hypertrophy modifiers / myokines (IL15RA, NTRK2, LRPPRC)	IL-15 ligand, BDNF, mitochondrial gene-expression coactivators.	Resistance training (induces IL-15); aerobic + strength combined for BDNF; no specific supplementation
Power / neural / vascular / connective (ACE, NOS3, BDNF, COL1A1, COL5A1, VDR, IL6)	Zn^{2+} (ACE, MMP3); BH4, arginine, NADPH, FAD/FMN, calmodulin (NOS3); vitamin C, copper, iron, zinc (collagen synthesis); 1,25-$(OH)_2$-D_3 (VDR).	Vitamin C 500 mg–2 g/d (collagen synthesis); copper-zinc balance; vitamin D sufficiency 25(OH)D 40–60 ng/mL; arginine/citrulline/nitrate for NO axis; collagen peptides 10–15 g pre-tendon-loading session (well-evidenced for tendon collagen synthesis, Shaw 2017 Am J Clin Nutr)

"Intervention target" means a substance, behavior, or pharmacology that addresses the relevant biochemistry. It does not mean every person should do every intervention listed. Personalization depends on individual genotype, baseline values, current clinical context, and goals.

5. Complete SNP Lookup Table

Quick reference for SNPs catalogued in this document, sorted by gene. Coordinates are GRCh38. Verify against your VCF's contig naming convention ("chr1" vs "1") before running positional lookups. Coordinates compiled from dbSNP build 156 and should be re-verified for the specific VCF build before use.

Gene	rsID	Variant name	GRCh38 coordinate	Risk / power-favoring allele
AR	(CAG)n	Exon 1 microsatellite	chrX:67545317-67545419	Long ≥21 repeats favorable for muscle (uncallable from SNP VCF)
AR	rs6152	E211E synonymous	chrX:67560815	G (X-linked, AGA-tag)
SHBG	rs1799941	G>A	chr17:7635476	A higher SHBG
SHBG	rs6259	D356N	chr17:7639095	A (N356) higher SHBG
CYP19A1	rs2470152	intronic T>C	chr15:51210647	Variable per cohort
CYP19A1	rs4646	3'UTR C>A	chr15:51208568	A
CYP17A1	rs743572	-34 T>C	chr10:102836835	C
MSTN	rs1805086	K153R, A>G	chr2:190058559	G (R153) muscle-favoring (rare)
MSTN	rs180108	A55T, G>A	chr2:190057583	A (T55) favorable in some studies

Gene	rsID	Variant name	GRCh38 coordinate	Risk / power-favoring allele
MSTN	rs11333758	indel −/−	chr2 ~190060000 region	−/− favorable (Polish elite)
ACVR1B	rs2854464	intron 7 A>G	chr12:51955710	G muscle-favoring
ACVR1B	rs10783485	intronic G>T	chr12:51953000 region	T muscle-favoring
ACVR2A	rs3764955	intronic G>C	chr2:147914000 region	CC and GG favorable
ACVR2B	rs2276541	intronic T>C	chr3:38469000 region	Mixed
FST	rs3797296	intronic	chr5:53464000 region	Less-replicated
ACTN3	rs1815739	R577X, C>T	chr11:66560624	C (R577) power-favoring
MYBPC3	rs1052373	V158M	chr11:47349148	Mixed
TTN	rs10497520	intronic	chr2:178525989	Weak grip-strength signal
CKM	rs8111989	NcoI 3'UTR A>G	chr19:45325300 region	Variable per cohort
AMPD1	rs17602729	Q12X, C>T	chr1:115223164	C (Q12) power-favoring
PPP1R3A	rs112443063	R905X premature stop	chr7:113716000 region	Reference allele favorable
CPNE5	rs3213537	intronic	chr6:36764000 region	Variant favorable for power
RPS6KB1	rs17158836	intronic	chr17:59995000 region	Less characterized
EIF4EBP1	rs1973700	intronic	chr8:38030000 region	Less characterized
MYC	rs6983267	intergenic 8q24	chr8:127401060	G cancer-associated
IL15RA	rs2228059	exon 7 1775 A>C	chr10:5993000 region	A favorable for hypertrophy
NTRK2	rs2289656	intronic	chr9:84671000 region	Less characterized
LRPPRC	rs10186876	intronic	chr2:43886000 region	Strength-associated
MMS22L	rs9320823	intronic	chr6:97580000 region	Strength-associated
PHACTR1	rs6905419	intronic	chr6:13019000 region	Strength-associated

Gene	rsID	Variant name	GRCh38 coordinate	Risk / power-favoring allele
GH1	rs2665802	promoter T>A	chr17:63920000 region	A favorable in FAMuSS
LEP	rs7799039	-2548 G>A promoter	chr7:128241000 region	A higher leptin
LEPR	rs1137101	Q223R	chr1:65592830	A (R223) modifier
FTO	rs9939609	intron 1 T>A	chr16:53786615	A obesity-risk; muscle CSA effect in elderly
PPARG	rs1801282	Pro12Ala C>G	chr3:12351626	C (Pro12) wildtype; G (Ala12) favorable RT response
MTHFR	rs1801133	C677T A>G in dbSNP	chr1:11796321	T (677T) reduces activity (cross-ref Homocysteine)
ACE	rs1799752	I/D Alu indel intron 16	chr17:63488530-63488817	D power-favoring (uncallable from SNP VCF)
ACE (tag)	rs4341	intronic G>C	chr17:63488530 region	G in LD with D allele
ACE (tag)	rs4342	intronic G>A	chr17:63488700 region	G in LD with D allele
ACE (tag)	rs4343	intronic G>A	chr17:63489000 region	G in LD with D allele
AGT	rs699	M235T T>C	chr1:230710048	T (235T) higher AGT
AGTR2	rs11091046	X-linked A>C	chrX:115306000 region	C favorable for power in males
NOS3	rs2070744	-786 T>C	chr7:150992991	C reduces eNOS expression
NOS3	rs1799983	G894T E298D	chr7:150999023	T (D298) reduced eNOS
BDNF	rs6265	Val66Met G>A	chr11:27658369	A (Met66) reduces secretion (unfavorable)
DRD2	rs1800497	Taq1A in ANKK1 G>A	chr11:113400106	A (Lys713) reduces D2 density
COMT	rs4680	Val158Met G>A	chr22:19963748	A (Met158) slower clearance
COL1A1	rs1800012	Sp1 site G>T (intron 1)	chr17:50201723	T protective for tendon injury (rare)
COL5A1	rs12722	3'UTR T>C	chr9:134842250	T injury-risk; C protective
COL5A1	rs13946	intronic T>C	chr9:134842500 region	Tag SNP

Gene	rsID	Variant name	GRCh38 coordinate	Risk / power-favoring allele
COL3A1	rs1800255	G>A	chr2:189011000 region	A less-replicated
MMP3	rs679620	E45K G>A	chr11:102837000 region	A modifier
IL6	rs1800795	-174 G>C	chr7:22727026	G higher IL-6 production
TNF	rs1800629	-308 G>A	chr6:31543031	A higher TNF
VEGFA	rs2010963	-634 G>C	chr6:43770083	C lower VEGF
VDR	rs2228570	FokI T>C (M1T)	chr12:47908762	C (F) truncated isoform
VDR	rs1544410	BsmI intronic A>G	chr12:47846052	G (B) favorable in some elderly cohorts
VDR	rs7975232	ApaI intronic	chr12:47845054	Haplotype-tag
VDR	rs731236	TaqI exon 9 T>C	chr12:47844974	Haplotype-tag
VDR	rs11568820	Cdx2 promoter A>G	chr12:47917373	G favorable for BMD

Coordinates above are approximate and compiled from dbSNP build 156 (GRCh38). Several positions are listed as "region" where the precise basepair varies by source — verify the exact coordinate in your VCF before running positional lookups. The ACE I/D Alu insertion and AR (CAG)n microsatellite require non-SNP genotyping methods (Sanger or fragment-length analysis from BAM). Indel-aware short-read calling (e.g., GATK HaplotypeCaller or DeepVariant) may detect the ACE 287-bp Alu in some VCFs but is unreliable; tag-SNP inference via rs4341/rs4342/rs4343 is the recommended workaround.

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