Endurance Training

Genetic Pathway Reference

10 Functional Categories • ~75 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of endurance exercise capacity, the genes that govern each node of the endurance phenotype, the well-studied common variants in those genes, the cofactors each enzyme or signaling component depends on, and the supplement and dietary targets that map to each cofactor and pathway. It is intended for use by clinicians, researchers, and athletes 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 large meta-analyses of athlete cohorts. 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 to 1.5); clinical significance arises from cumulative patterns and gene–training interactions. A small number of variants — notably ACE I/D, ACTN3 R577X, AMPD1 c.34C>T, PPARGC1A Gly482Ser, and the high-altitude EPAS1/EGLN1 haplotypes — have larger and clinically actionable effect sizes.

Heritability framework. Baseline VO_2max has a heritability of approximately 50%. VO_2max trainability — the gain in VO_2max in response to a standardized training stimulus — has a heritability of approximately 47% in the HERITAGE Family Study (Bouchard et al., J Appl Physiol 1999), with a range of −114 to +1097 mL/min after 20 weeks of moderate-intensity continuous training in 473 sedentary adults. A subsequent GWAS identified 39 SNPs at $p < 1.5\times10^{-4}$; the top 21 explained approximately 49% of trainability variance in a polygenic predictor score (Bouchard et al., J Appl Physiol 2011). Twin and athlete-cohort studies estimate that additive genetic factors account for roughly 66% of variance in elite athlete status (Varillas-Delgado, Genes 2024). The single largest replicable common-variant signals lie at ACE, ACTN3, AMPD1, and PPARGC1A.

2. Pathway Biology

2.1 What endurance is, mechanistically

Endurance is the capacity to sustain submaximal aerobic work over time without unsustainable accumulation of fatigue. It is defined physiologically by three master variables: maximal oxygen uptake (VO_2max), lactate threshold (the workload above which lactate accumulates faster than it clears), and exercise economy (the oxygen cost per unit of external work). VO_2max sets the ceiling, lactate threshold sets the sustainable fraction of that ceiling, and economy sets the work performed per unit of oxygen consumed. World-class endurance performance requires excellence in all three, and each has its own genetic architecture.

VO_2max itself is the product of cardiac output (heart rate × stroke volume) multiplied by arteriovenous oxygen difference. This decomposition matters because it identifies the two

distinct upstream constraints: oxygen delivery (cardiovascular plumbing, hemoglobin mass, capillarization) and oxygen utilization (mitochondrial density and enzyme content in skeletal muscle). Genes contribute to both, and the relative contribution of each constraint differs across individuals.

2.2 The four transport stages of oxygen

Oxygen travels from atmosphere to mitochondrion through four serial conductances, each with genetic modifiers. Stage 1 — pulmonary diffusion — is governed by alveolar surface area and capillary perfusion, with relatively limited common-variant signal. Stage 2 — circulatory transport — depends on cardiac output, blood volume, hemoglobin concentration, and vascular tone. Stage 3 — capillary diffusion — depends on capillary density and red cell transit time, both modifiable by training and angiogenic gene expression. Stage 4 — mitochondrial extraction — depends on mitochondrial volume, oxidative enzyme content, and substrate availability. Endurance training expands every stage simultaneously, but the relative gain at each stage varies with genotype.

2.3 The PGC-1α master switch

Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α, encoded by PPARGC1A) is the central node of the endurance adaptation response. Acute exercise activates PGC-1α through four converging signals: AMPK (responding to AMP/ATP ratio), p38 MAPK (responding to mechanical and oxidative stress), calcineurin–CaMK (responding to calcium transients), and SIRT1 (responding to NAD^+/NADH ratio). PGC-1α then coactivates a network of transcription factors — NRF1 (nuclear respiratory factor 1), GABPA/B (the protein originally named NRF2 of mitochondrial biogenesis, distinct from the NFE2L2 antioxidant transcription factor also called NRF2), TFAM (mitochondrial transcription factor A), ERR-α, and PPAR-α/δ — to drive transcription of genes encoding mitochondrial proteins, β-oxidation enzymes, fiber-type switches, and angiogenic factors including VEGF (Lin et al., Cell Metab 2005; Liang & Ward, Adv Physiol Educ 2006).

Two terminological points deserve emphasis. First, PGC-1α is a coactivator, not a transcription factor — it has no DNA-binding domain and acts only by docking onto partner factors. Second, the literature contains two unrelated proteins called NRF2: NFE2L2 (the Keap1-regulated antioxidant transcription factor) and GABPA/GABPB1 (the heterodimeric mitochondrial-biogenesis transcription factor originally named nuclear respiratory factor 2). This document distinguishes them throughout.

2.4 The HIF oxygen-sensing axis

Cells sense oxygen tension through prolyl hydroxylases (encoded by EGLN1/2/3, also called PHD1/2/3) that hydroxylate two proline residues on hypoxia-inducible factor α subunits (HIF-1α encoded by HIF1A, HIF-2α encoded by EPAS1). Hydroxylated HIF-α is recognized by the von Hippel-Lindau (VHL) E3 ubiquitin ligase and degraded by the proteasome. Under hypoxia, hydroxylase activity falls, HIF-α stabilizes, dimerizes with HIF-β (ARNT), and transactivates target genes including erythropoietin (EPO), vascular endothelial growth factor (VEGFA), glucose transporters, and most glycolytic enzymes (Semenza, Annu Rev Pathol 2014). The hydroxylases require iron, ascorbate, and 2-oxoglutarate — all three are nutritional cofactors with direct relevance to endurance physiology.

The Tibetan and Andean high-altitude adaptations are the most striking natural experiments in this pathway. Tibetan-specific variants in EPAS1 (Yi et al., Science 2010; Beall et al., PNAS

2010; Simonson et al., Science 2010) and EGLN1 (Lorenzo et al., Nat Genet 2014) blunt the polycythemic response to chronic hypoxia, allowing sustained physical performance at altitude without the cardiovascular cost of hyperviscous blood. Andean populations independently acquired a different EPAS1 missense variant achieving partly convergent phenotypes (Crawford et al., Sci Adv 2024). These variants are essentially absent in European-ancestry populations.

2.5 The fiber-type axis

Skeletal muscle fibers exist on a continuum from slow-twitch oxidative (type I, MYH7) through fast-twitch oxidative-glycolytic (type IIa, MYH2) to fast-twitch glycolytic (type IIx, MYH1). Type I fibers are mitochondria-rich, capillary-rich, and fatigue-resistant; type IIx fibers generate higher peak force and power but fatigue rapidly. Elite endurance athletes carry 70 to 95 percent type I fibers in vastus lateralis biopsies; elite sprinters carry the inverse. Although the absolute fiber-type proportion is largely fixed in adulthood, training shifts the IIa/IIx balance and the oxidative capacity of all fiber types. The single most-studied variant in sports genomics, ACTN3 R577X, modifies this axis by determining whether α-actinin-3 is expressed in fast-twitch fibers — XX null individuals lack the protein and exhibit a metabolic shift toward oxidative phenotype, while RR carriers retain the original fast-twitch architecture (MacArthur et al., Hum Mol Genet 2008; Eynon et al., Sports Med 2013).

2.6 The substrate-utilization axis

At submaximal work, muscle oxidizes a mixture of carbohydrate (glucose from blood and glycogen from muscle) and fat (intramuscular triglyceride and circulating fatty acids). The fat-to-carbohydrate ratio at a given absolute workload is a measure of metabolic flexibility. Endurance training shifts this ratio toward fat, sparing limited glycogen for higher intensities. PPAR-δ (PPARD) is the master transcription factor for muscle fat oxidation, induced by exercise and by long-chain fatty acids; transgenic activation of PPAR-δ in mouse muscle produces a marathon-runner phenotype with increased type I fibers and dramatically increased endurance (Wang et al., PLoS Biol 2004). β2-adrenergic signaling (ADRB2) governs lipolysis from adipose tissue during exercise; common Arg16Gly and Gln27Glu variants modify receptor downregulation and lipolytic response, with inconsistent but real effects on substrate utilization. AMP deaminase 1 (AMPD1) catalyzes AMP → IMP + NH_3 during high-energy demand, supporting the purine nucleotide cycle and ATP regeneration; the c.34C>T nonsense variant produces a non-functional enzyme and is associated with reduced exercise capacity and overrepresented in non-athletes versus athletes.

2.7 The lactate-shuttle axis

Lactate is produced continuously by glycolysis and oxidized continuously by mitochondria. Net accumulation occurs only when production exceeds clearance. Lactate is exported from glycolytic fibers and the cytosol via monocarboxylate transporter 4 (MCT4, SLC16A3), and imported into oxidative fibers, heart, and brain via monocarboxylate transporter 1 (MCT1, SLC16A1) for oxidation. The lactate-threshold workload is a function of both the rate of glycolytic flux and the capacity of MCT1 to clear lactate. The SLC16A1 rs1049434 variant produces a substitution at amino acid 490 that modifies transport activity; the A allele is associated with endurance performance and lower post-exercise blood lactate in multiple cohorts (Sawczuk et al., Eur J Appl Physiol 2015).

2.8 The redox axis

Acute exercise generates reactive oxygen species at the mitochondrial electron transport chain, NADPH oxidases, and xanthine oxidase. At physiological levels these ROS act as signaling molecules that drive adaptation — the mitohormesis paradigm — including PGC-1α induction, NFE2L2 (Nrf2) activation, and capillary growth. Excess ROS, conversely, damage proteins, lipids, and DNA, and can blunt adaptation. NFE2L2 is the master transcription factor of antioxidant response, sequestered in the cytoplasm by Keap1 under basal conditions; ROS oxidation of Keap1 cysteines releases NFE2L2 to translocate to the nucleus and bind antioxidant response elements (AREs) upstream of glutathione synthesis enzymes, peroxiredoxins, and phase-II detoxifiers. NFE2L2-knockout mice have reduced exercise-induced mitochondrial biogenesis, blunted antioxidant gene expression, and impaired exercise capacity (Merry & Ristow, J Physiol 2016). The supplement-target intersection includes selenium (GPX cofactor), manganese (SOD2 cofactor), N-acetylcysteine and glycine (glutathione substrate), sulforaphane and astaxanthin (NFE2L2 activators).

2.9 The brain–muscle axis

Central fatigue is biological, not metaphorical. It is mediated by serotonergic and dopaminergic signaling, BDNF-driven hippocampal plasticity, and cerebral lactate uptake. Endurance training is one of the most potent known stimuli of brain-derived neurotrophic factor (BDNF) in the hippocampus, with effect sizes comparable to selective serotonin reuptake inhibitors in some cognitive endpoints. The mechanistic link runs PGC-1α → FNDC5 → cleaved irisin → hippocampal BDNF, providing a direct molecular bridge from skeletal muscle to brain (Wrann et al., Cell Metab 2013). The BDNF Val66Met variant impairs activity-dependent BDNF secretion (Egan et al., Cell 2003) and reduces exercise-induced neurogenesis in mouse Met knock-in models (Ieraci et al., Neuropsychopharmacol 2016), though human studies on exercise–cognition interactions are mixed (de Las Heras et al., Front Aging Neurosci 2020 review).

2.10 The iron axis

Iron is the most-trafficked transition metal in endurance physiology: it sits at the catalytic core of hemoglobin, myoglobin, all cytochromes of the electron transport chain, the mitochondrial Fe-S clusters, and the prolyl hydroxylases of the HIF axis. Iron deficiency reduces VO_2max independent of hemoglobin (via tissue-level mitochondrial iron). Conversely, iron overload is genuinely toxic to endurance — mitochondrial iron loading drives oxidative damage and may be a long-term risk in HFE C282Y homozygotes who superficially appear to perform well in their twenties and thirties but accumulate parenchymal damage over decades. The hepcidin–ferroportin axis is the master regulator: hepcidin (HAMP) produced by the liver in response to iron stores, inflammation, and BMP6 signaling binds ferroportin on duodenal enterocytes and macrophages, inducing its internalization and degradation. Acute exercise transiently raises hepcidin (via IL-6) and can blunt iron absorption in the post-exercise window — relevant for athletes attempting to correct iron deficiency.

3. Functional Categories and Gene Catalog

3.1 Cardiovascular plumbing — renin-angiotensin and bradykinin

The renin-angiotensin system controls vascular tone and salt-water balance; the bradykinin system modulates capillary permeability and exercise-induced vasodilation. The ACE I/D indel is the single most-studied variant in sports genetics.

Gene	rsID / variant	Functional consequence	Cofactor / node
ACE	rs1799752 (I/D), rs4340 tag	I (insertion) allele lower ACE activity, lower angiotensin II, more bradykinin. II OR 1.54 (95% CI 1.24–1.91) for elite endurance vs controls; OR 1.76 in runners, 2.69 in triathletes (Sommers et al., IJERPH 2024).	Zn^{2+} (catalytic)
AGT	rs699 (M235T)	T allele raises plasma angiotensinogen; weak endurance association.	Renin substrate
AGTR1	rs5186 (A1166C)	C allele alters AT1 receptor signaling; mixed endurance evidence.	Angiotensin II receptor
BDKRB2	rs1799722 (-58T/C)	+9 (T) allele higher transcription, enhanced bradykinin signaling; modestly favorable for endurance (Saunders et al., J Physiol 2006).	Bradykinin B2 receptor
NOS3	rs1799983 (G894T, E298D)	Asp allele lower eNOS protein, lower basal NO, lower exercise-induced flow-mediated dilation.	BH_4, NADPH, FAD/FMN
NOS3	rs2070744 (-786T/C)	C allele lower eNOS transcription.	Same as above
EDN1	rs5370 (K198N)	Asn allele higher endothelin-1, higher BP at exercise.	Vasoconstrictor peptide

This category overlaps the Endothelial Health pathway. The ACE I/D indel may not be reliably called from short-read SNP-only VCFs and typically requires a positional or PCR-based assay; the rs4340 tag SNP provides a partial proxy.

3.2 Oxygen sensing and erythropoiesis — the HIF axis

HIF-α subunits are continuously hydroxylated by EGLN/PHD enzymes and degraded; under hypoxia they stabilize and induce EPO, VEGF, and glycolytic genes.

Gene	rsID / variant	Functional consequence	Cofactor / node
HIF1A	rs11549465 (P582S)	Ser allele more stable HIF-1α; elite endurance association in some cohorts (Döring et al., J Appl Physiol 2010).	Fe^{2+}, 2-oxoglutarate, O_2 (PHD substrate)
HIF1A	rs11549467 (A588T)	Functional missense; rare.	Same as above
EPAS1 (HIF2A)	rs13419896, rs4953354,	Tibetan-selected SNPs; lower EPAS1 expression → blunted polycythemia at altitude	Fe^{2+}, 2-OG, O_2

Gene	rsID / variant	Functional consequence	Cofactor / node
	rs1868092	(Yi et al., Science 2010; Beall et al., PNAS 2010).	
EGLN1 (PHD2)	rs186996510, rs12097901	Tibetan-selected coding variants modify hydroxylase activity (Lorenzo et al., Nat Genet 2014).	Fe^{2+}, ascorbate, 2-OG
VHL	various rare	Loss-of-function causes Chuvash polycythemia.	E3 ubiquitin ligase
EPO	rs1617640 (-1306T/G)	Promoter; modest serum EPO effect.	Erythropoietin protein
EPOR	rare gain-of-function	Causes primary familial polycythemia (Mäntyselkä et al., Br J Haematol 2017).	EPO receptor

Cofactor-relevant supplement targets in this category: iron (PHD/EGLN active site), ascorbate, and 2-oxoglutarate–precursor amino acids. Iron status is the single most modifiable input to oxygen-carrying capacity in endurance athletes.

3.3 Mitochondrial biogenesis — the PGC-1α coactivator network

Exercise-induced activation of PGC-1α drives transcription of mitochondrial proteins via NRF1, GABPA/B, TFAM, ERR-α, and PPAR-α/δ partner factors.

Gene	rsID / variant	Functional consequence	Effect / node
PPARGC1A	rs8192678 (G482S)	Ser allele lower PGC-1α activity. Gly/Gly OR 1.19–1.30 for elite endurance status in Caucasians (Su et al., Front Physiol 2025; Chen et al., Biol Sport 2019, n=3,708 athletes).	PGC-1α coactivator
PPARGC1A	rs17110656	Promoter variant; less-replicated.	PGC-1α expression
PPARA	rs4253778 (intron 7 G/C)	C allele endurance-associated; G favors power (Ahmetov et al., Hum Genet 2006).	PPAR-α; β-oxidation
PPARD	rs2016520 (T294C)	Inconsistent alone; PPARD CC + PPARGC1A Gly/Gly combined OR 8.32 for elite endurance (Eynon et al., Scand J Med Sci Sports 2010).	PPAR-δ ligand-binding
NRF1	rs6949152	A/A in women associated with higher type-I fiber proportion (Yvert et al., Front Physiol 2016).	Mitochondrial transcription factor
GABPB1 (mtNRF2)	rs7181866	Heterozygous AG overrepresented in elite endurance (Eynon et al., J Appl Physiol 2009). Distinct from NFE2L2/NRF2.	Mitochondrial transcription factor
GABPB1 (mtNRF2)	rs8031031	Linked endurance signal.	Same as above
TFAM	rs1937 (S12T)	Mixed evidence; mtDNA copy number.	mtDNA replication

Gene	rsID / variant	Functional consequence	Effect / node
ESRRA	rs6573 / others	ERR-α; less-studied PGC-1α partner.	Steroid receptor
NRF2 (NFE2L2, antioxidant)	rs6721961 (-617 C/A)	A allele lower promoter activity; redox category, not mitochondrial biogenesis.	Antioxidant transcription

PPARGC1A Gly482Ser is the most-replicated mitochondrial-axis endurance signal. Note the two distinct "NRF2" proteins: GABPA/GABPB1 (mitochondrial-biogenesis transcription factor, this section) and NFE2L2 (Keap1-regulated antioxidant transcription factor, section 3.7).

3.4 Skeletal muscle structure — fiber type and sarcomere

Slow-twitch (type I) and fast-twitch (type II) fibers differ in mitochondrial content, capillarization, and fatigue resistance. ACTN3 R577X modifies fast-fiber metabolism.

Gene	rsID / variant	Functional consequence	Effect / node
ACTN3	rs1815739 (R577X, C1747T)	X (T) is a premature stop codon; XX null carriers lack α-actinin-3 in fast fibers, with metabolic shift toward oxidative phenotype. X allele OR 1.32 endurance vs power; XX OR 1.59 (CI 1.32–1.92) endurance vs power (El Ouali et al., Sports Med Open 2024).	Z-line scaffold (fast fibers)
MSTN	rs1805086 (K153R)	R rare; loss-of-function causes muscle hyperplasia.	Myostatin
MYH7	various rare	β-MHC slow; rare variants cause hypertrophic cardiomyopathy.	Slow myosin heavy chain
CKM	rs8111989 (NcoI A/G)	Muscle creatine kinase; meta-analyses link polymorphism to VO_2max variation (Heled et al., 2007; Fedotovskaya et al., 2014). G allele endurance-associated in some cohorts.	Creatine phosphate shuttle
IGF1	rs35767 (C-1245T)	Modest exercise-response signal (covered in IGF1 report)	IGF-1 signaling
IL15RA	rs2296135 (A/C)	Modest signal for muscle hypertrophy / fiber type.	IL-15 receptor α

ACTN3 is the single most-studied variant in sports genomics. The XX (null) allele is overrepresented in endurance athletes versus power athletes, but the contrast versus non-athlete controls is more modest — XX is favorable for endurance not because it is athletically advantageous in absolute terms, but because RR is more strongly disadvantageous for endurance relative to power.

3.5 Substrate utilization — fat versus carbohydrate during exercise

Endurance-trained muscle oxidizes a higher fraction of fat at the same absolute workload. β-adrenergic signaling, fatty acid handling, and AMP deamination all modulate this balance.

Gene	rsID / variant	Functional consequence	Cofactor / node
ADRB2	rs1042713 (Arg16Gly)	Gly16 increased agonist-induced downregulation; Arg16 sustained response. Arg16 associated with higher peak VO_2 in heart failure (Wagoner et al., Circ Heart Fail 2000); inconsistent in healthy athletes (Jocken et al., Diabetologia 2007, n=7,808).	β2 adrenergic receptor
ADRB2	rs1042714 (Gln27Glu)	Glu27 relative resistance to downregulation; modulates lipolysis and exercise responsiveness in some studies (Borgo Faria et al., Gene 2022).	β2 adrenergic receptor
ADRB2	rs1800888 (Thr164Ile)	Rare loss-of-function; reduced agonist binding.	Same
AMPD1	rs17602729 (c.34C>T, Q12X)	T (X) allele = nonsense → AMPD1 deficiency. CC overrepresented in endurance athletes, OR 1.72 (CI 1.40–2.12); TT essentially absent in athletes (El Ouali et al., Sports Med Open 2025, n=5,717).	AMP deaminase
FABP2	rs1799883 (A54T)	Thr higher fat absorption; modest endurance/metabolic association.	Intestinal fatty acid binding protein
LIPC	rs1800588 (-514 C/T)	T promoter variant, lower hepatic lipase.	Hepatic lipase
LPL	rs328 (S447X)	X allele higher LPL activity, lower TG; modest endurance signal.	Lipoprotein lipase

AMPD1 c.34C>T is recessive: only TT homozygotes are protein-deficient, and they are essentially absent from athletic populations. CT heterozygotes have intermediate enzyme activity but show only modest performance reduction.

3.6 Lactate handling — the lactate shuttle

Lactate is a fuel, not a waste product. The capacity to import lactate into oxidative tissues via MCT1 sets the lactate threshold.

Gene	rsID / variant	Functional consequence	Cofactor / node
SLC16A1 (MCT1)	rs1049434 (A1470T, E490D)	T (D) allele lower transport activity; A allele endurance-associated and lower post-exercise lactate (Sawczuk et al., Eur J Appl Physiol 2015).	H^+-monocarboxylate cotransporter
SLC16A3 (MCT4)	rare variants	Lactate export from glycolytic fibers; less-studied common variants.	H^+-monocarboxylate cotransporter
LDHA / LDHB	various	Lactate dehydrogenase; isoform ratio shifts with training.	NAD^+ / NADH
BSG (CD147)	rare variants	MCT1 chaperone required for membrane localization.	Ig superfamily

3.7 Antioxidant defense and redox signaling — NFE2L2 / Nrf2 axis

Acute exercise generates ROS that drive adaptation; chronic excess damages mitochondria. NFE2L2 (the antioxidant Nrf2, distinct from GABPA/B mtNRF2 of section 3.3) is the master antioxidant transcription factor.

Gene	rsID / variant	Functional consequence	Cofactor / node
NFE2L2 (Nrf2)	rs6721961 (-617 C/A)	A allele lower NFE2L2 promoter activity; modest cardiovascular signals; sparse endurance studies.	Cysteine; Keap1 redox sensor
NFE2L2	rs2364722, rs6706649	Promoter / intronic variants modulating expression.	Same
KEAP1	rs11085735, rs9676881	Cytoplasmic NFE2L2 inhibitor; less-studied common variants.	Cul3 E3 ligase complex
SOD2	rs4880 (V16A, A16V)	Ala/Ala higher mitochondrial import efficiency, lower oxidative damage.	Mn^{2+}
SOD3	rs1799895 (R213G)	Extracellular SOD; rare but functional.	Cu^{2+} / Zn^{2+}
GPX1	rs1050450 (P198L)	Leu allele lower GPX activity.	Selenium, GSH
CAT	rs1001179 (-262 C/T)	T promoter variant, lower catalase.	Heme
NQO1	rs1800566 (P187S)	Ser allele reduced NQO1 activity; ROS clearance.	FAD

Reprised from Glucose, Endothelial, and Glycation pathway references — the redox bottleneck threads through every metabolic genetic profile. Cofactor-relevant supplement targets: selenium (GPX), manganese (SOD2), N-acetylcysteine and glycine (glutathione substrate), sulforaphane and astaxanthin (NFE2L2/Nrf2 activators).

3.8 Brain and neuromuscular drive

Central fatigue and exercise-induced neuroplasticity are governed by BDNF, dopaminergic and serotonergic signaling, and the muscle-to-brain irisin axis.

Gene	rsID / variant	Functional consequence	Cofactor / node
BDNF	rs6265 (V66M, Val66Met)	Met allele reduces activity-dependent BDNF secretion (Egan et al., Cell 2003); Met carriers show smaller exercise-induced BDNF response in some studies (Hopkins et al., 2012); mixed cognitive results (de Las Heras et al., 2020 review).	TrkB receptor
FNDC5	rs16835198, rs726344	Encodes irisin precursor cleaved from FNDC5; PGC-1α target linking muscle to brain BDNF (Wrann et al., Cell Metab 2013).	Irisin / BDNF
COMT	rs4680 (V158M)	Met/Met lower prefrontal dopamine catabolism, higher cortical DA tone — "warrior vs worrier" cognitive phenotype; modest pacing/fatigue tolerance signal.	Mg^{2+}, SAM

Gene	rsID / variant	Functional consequence	Cofactor / node
DRD2	rs1800497 (Taq1A)	A1 allele lower D2 density; reward and motor control.	Dopamine D2 receptor
TPH2	rs4570625 (-703 G/T)	Tryptophan hydroxylase 2; brain serotonin synthesis.	BH_4, Fe^{2+}
SLC6A4	5-HTTLPR	Serotonin transporter promoter; S allele lower expression.	Serotonin reuptake
HTR2A	rs6313 (T102C)	Serotonin 2A receptor; central fatigue modulation.	Gq-coupled GPCR
MAOA	uVNTR (3 vs 4 repeats)	Monoamine oxidase A; degrades 5-HT, NE, DA.	FAD

Most evidence in this category comes from cognitive and psychiatric studies; direct endurance-performance evidence is thinner. The strongest exercise-relevant signal is BDNF rs6265 for the magnitude of exercise-induced BDNF release.

3.9 Pharmacogenomic ergogenics — caffeine response

Caffeine is the best-evidenced legal ergogenic aid for endurance. CYP1A2 metabolizes >95% of ingested caffeine; ADORA2A encodes the central A2A adenosine receptor that caffeine antagonizes.

Gene	rsID / variant	Functional consequence	Effect / node
CYP1A2	rs762551 (-163 A/C)	AA = fast metabolizer (faster CYP1A2 induction); AC/CC = slow metabolizer. In 101 athletes: caffeine 2 and 4 mg/kg improved 10-km cycling time only in AA homozygotes; 4 mg/kg worsened CC times (Guest et al., MSSE 2018). Replications mixed.	Heme; Phase I CYP
ADORA2A	rs5751876 (T/C)	TT "high sensitivity" to caffeine; CT/CC "low sensitivity." Endurance evidence in women (Loy et al., 2015); studies generally small.	Adenosine A2A receptor
AHR	rs2066853 (R554K)	Aryl hydrocarbon receptor; CYP1A2 inducer. Modest caffeine-clearance modifier.	Transcription factor

3.10 Iron handling — the HFE / hepcidin axis

Iron deficiency reduces VO_2max independent of hemoglobin (via tissue-level mitochondrial iron). Iron overload is mitochondrially toxic over decades; HFE C282Y is the most common cause of hereditary hemochromatosis and is enriched in some endurance athlete populations because young carriers superficially benefit from elevated iron stores.

Gene	rsID / variant	Functional consequence	Cofactor / node
HFE	rs1800562 (C282Y)	Y/Y homozygotes have >80% lifetime risk of biochemical iron overload, ~30% develop clinical hemochromatosis (Allen et al., NEJM 2008).	Class I MHC-like; β2-microglobulin

Gene	rsID / variant	Functional consequence	Cofactor / node
		Heterozygotes have modestly elevated transferrin saturation. Some endurance enrichment reported (Chicharro et al., Br J Sports Med 2004).	partner
HFE	rs1799945 (H63D)	Compound heterozygotes (C282Y/H63D) have intermediate phenotype.	Same
TFR2	rare variants	Transferrin receptor 2; rare hereditary hemochromatosis type 3.	Iron sensing
TMPRSS6	rs855791 (V736A)	Matriptase-2; A allele higher hepcidin → lower iron absorption; associated with lower hemoglobin and iron deficiency anemia (Benyamin et al., Nat Genet 2009).	Serine protease (BMP6 axis)
TF (transferrin)	rs3811647	Plasma transferrin levels.	Iron-binding protein
HAMP	rs10421768	Hepcidin promoter; rare loss-of-function causes juvenile hemochromatosis.	Hepcidin

HFE C282Y/Y in endurance athletes is a chronic-risk paradox: superficially performance-favorable through the third or fourth decade because elevated iron stores support hemoglobin and oxidative metabolism, but with rising risk of liver, joint, and cardiac iron deposition over later decades. Phlebotomy is curative if identified early. Annual ferritin and transferrin saturation monitoring is warranted in homozygotes regardless of athletic status.

3.11 Cardiac safety — common variants and screening considerations

This brief category covers the structural and electrical genes that intersect endurance training with cardiac safety. Common variants are weak; the relevant signals are rare pathogenic variants in inherited cardiomyopathy and channelopathy genes that can underlie exercise-associated sudden cardiac death. Routine sports cardiology screening (12-lead ECG, often echocardiogram) outperforms common-variant genotyping for this purpose; the genes are listed for completeness.

Gene	Phenotype if pathogenic variant	Common-variant endurance signal
MYH7	Hypertrophic cardiomyopathy (HCM)	None replicable
MYBPC3	Hypertrophic cardiomyopathy (HCM)	None replicable
TTN	Dilated cardiomyopathy (truncating variants)	rs2562846 weak fitness signal
RYR2	CPVT (catecholaminergic polymorphic VT)	Rare; not common-variant
KCNQ1, KCNH2, SCN5A	Long QT syndromes 1/2/3	None for endurance
DSP, PKP2, DSG2, DSC2	Arrhythmogenic right ventricular cardiomyopathy (exercise-triggered)	Not common-variant
LMNA	Dilated cardiomyopathy with conduction disease	None for endurance

Gene	Phenotype if pathogenic variant	Common-variant endurance signal
MYBPC3, MYH7, TPM1	Combined HCM panel	None for endurance

Whole-genome sequencing at 60× depth provides reasonable coverage for detection of exonic SNVs in these genes, but indels, copy-number variants, and intronic splice variants may be missed and require dedicated analysis pipelines (e.g., ClinVar-annotated variant calling, exome reanalysis). For competitive endurance athletes, ACC/AHA and ESC consensus statements recommend cardiology evaluation before genetic interpretation, not the reverse.

4. Cofactor and Supplement-Target Summary

This table consolidates the cofactor or substrate dependencies catalogued above. It does not constitute a recommendation; it identifies which biological levers exist for each pathway category. Personalization depends on individual genotype, intake, lab values, and clinical context.

Pathway category	Genes / enzymes	Cofactor / substrate	Supplement target
NO synthesis (eNOS)	NOS3	BH_4, NADPH, FAD, FMN, L-arginine	L-citrulline, L-arginine, folate (BH_4 sparing)
HIF / oxygen sensing	EGLN1/2/3, HIF1A, EPAS1	Fe^{2+}, ascorbate, 2-oxoglutarate, O_2	Iron (if deficient), vitamin C, αKG
Erythropoiesis / Hb	EPO, HBB, HFE, TMPRSS6	Iron, B12, folate, copper	Iron (if deficient), B12, folate; avoid excess if HFE+
PGC-1α / mitochondrial biogenesis	PPARGC1A, PPARA, PPARD, NRF1, GABPA/B, TFAM, ESRRA	NAD^+, SAM, acetyl-CoA, ATP	Nicotinamide riboside / NMN, exercise itself
β-oxidation	PPARA, ACADM, CPT1B, CPT2	Carnitine, FAD, NAD^+, CoQ10	L-carnitine, ubiquinol (CoQ10), riboflavin
Sarcomere / ATP recycling	ACTN3, CKM, AMPD1	Creatine, phosphate, ATP	Creatine monohydrate
Lactate shuttle	SLC16A1 (MCT1), SLC16A3 (MCT4)	H^+ gradient, pyruvate, lactate	Sodium bicarbonate (acute); β-alanine (carnosine buffer)
Antioxidant defense / Nrf2	NFE2L2, KEAP1, SOD2, SOD3, GPX1, CAT, NQO1	GSH, Mn^{2+}, Cu^{2+}/Zn^{2+}, selenium, FAD	NAC + glycine, selenium, manganese, sulforaphane, astaxanthin
Brain BDNF / dopamine	BDNF, FNDC5, COMT, DRD2, TPH2, MAOA, SLC6A4	BH_4, Mg^{2+}, SAM, Fe^{2+}	Magnesium, methylated B-vitamins (cofactor for COMT/TPH2)
Caffeine PK/PD	CYP1A2, ADORA2A, AHR	Heme; adenosine receptor	Caffeine timing/dose adjusted by genotype

Pathway category	Genes / enzymes	Cofactor / substrate	Supplement target
Iron handling	HFE, TMPRSS6, TFR2, HAMP, TF	Iron, ascorbate, BMP6	Iron (only if labs justify); avoid excess if HFE+

This table is a map of where each pathway intersects nutrition; it does not mean every person should supplement everything listed. Personalization depends on individual genotype, intake, lab values, and clinical context.

5. Complete SNP Lookup Table

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

Gene	rsID	GRCh38 position	Category
ACE	rs1799752 (I/D)	17:63488530 (indel)	Cardiovascular
ACE	rs4340 (tag)	17:63488544	Cardiovascular
ADORA2A	rs5751876	22:24423693	Pharmacogenomics
ADRB2	rs1042713 (R16G)	5:148826877	Substrate utilization
ADRB2	rs1042714 (Q27E)	5:148826910	Substrate utilization
ADRB2	rs1800888 (T164I)	5:148827322	Substrate utilization
AGT	rs699 (M235T)	1:230710048	Cardiovascular
AGTR1	rs5186 (A1166C)	3:148742201	Cardiovascular
AHR	rs2066853 (R554K)	7:17345242	Pharmacogenomics
AMPD1	rs17602729 (Q12X)	1:114681589	Substrate utilization
BDKRB2	rs1799722 (-58T/C)	14:96197145	Cardiovascular
BDNF	rs6265 (V66M)	11:27658369	Brain / neuromuscular
CAT	rs1001179 (-262C/T)	11:34438684	Antioxidant defense
CKM	rs8111989 (NcoI)	19:45307032	Sarcomere / muscle
COMT	rs4680 (V158M)	22:19963748	Brain / neuromuscular
CYP1A2	rs762551 (-163A/C)	15:74749576	Pharmacogenomics
DRD2	rs1800497 (Taq1A)	11:113400106	Brain / neuromuscular
EDN1	rs5370 (K198N)	6:12290677	Cardiovascular
EGLN1	rs186996510	1:231474449	HIF / oxygen sensing
EGLN1	rs12097901	1:231482484	HIF / oxygen sensing
EPAS1	rs13419896	2:46571408	HIF / oxygen sensing

Gene	rsID	GRCh38 position	Category
EPAS1	rs4953354	2:46612079	HIF / oxygen sensing
EPAS1	rs1868092	2:46606229	HIF / oxygen sensing
EPO	rs1617640 (-1306T/G)	7:100720800	HIF / oxygen sensing
ESRRA	rs6573	11:64310306	Mitochondrial biogenesis
FABP2	rs1799883 (A54T)	4:120241902	Substrate utilization
FNDC5	rs16835198	1:32867957	Brain / neuromuscular
FNDC5	rs726344	1:32859895	Brain / neuromuscular
GABPB1	rs7181866	15:50578774	Mitochondrial biogenesis
GABPB1	rs8031031	15:50571820	Mitochondrial biogenesis
GPX1	rs1050450 (P198L)	3:49357401	Antioxidant defense
HAMP	rs10421768	19:35282128	Iron handling
HFE	rs1800562 (C282Y)	6:26092913	Iron handling
HFE	rs1799945 (H63D)	6:26090951	Iron handling
HIF1A	rs11549465 (P582S)	14:61748591	HIF / oxygen sensing
HIF1A	rs11549467 (A588T)	14:61748609	HIF / oxygen sensing
HTR2A	rs6313 (T102C)	13:46831565	Brain / neuromuscular
IGF1	rs35767 (-1245C/T)	12:102481793	Sarcomere / muscle
IL15RA	rs2296135	10:5863471	Sarcomere / muscle
KEAP1	rs11085735	19:10491626	Antioxidant defense
KEAP1	rs9676881	19:10491931	Antioxidant defense
LDHA	rs10134657 (region)	11:18394163	Lactate handling
LIPC	rs1800588 (-514C/T)	15:58431520	Substrate utilization
LPL	rs328 (S447X)	8:19962213	Substrate utilization
MAOA	uVNTR	X:43654908 (region)	Brain / neuromuscular
MSTN	rs1805086 (K153R)	2:190058013	Sarcomere / muscle
MYH7	(panel)	14:23412910 (gene)	Sarcomere / cardiac
NFE2L2	rs6721961 (-617C/A)	2:177263443	Antioxidant defense
NFE2L2	rs2364722	2:177265529	Antioxidant defense
NFE2L2	rs6706649	2:177263363	Antioxidant defense
NOS3	rs1799983 (E298D)	7:150999023	Cardiovascular
NOS3	rs2070744 (-786T/C)	7:150992991	Cardiovascular
NQO1	rs1800566 (P187S)	16:69711242	Antioxidant defense

Gene	rsID	GRCh38 position	Category
NRF1	rs6949152	7:129815893	Mitochondrial biogenesis
PPARA	rs4253778	22:46258064	Mitochondrial biogenesis
PPARD	rs2016520 (T294C)	6:35413892	Substrate / mitochondrial
PPARGC1A	rs8192678 (G482S)	4:23814455	Mitochondrial biogenesis
PPARGC1A	rs17110656	4:23791884	Mitochondrial biogenesis
SLC16A1 (MCT1)	rs1049434 (E490D)	1:112929510	Lactate handling
SLC6A4	5-HTTLPR	17:30236098 (region)	Brain / neuromuscular
SOD2	rs4880 (V16A)	6:159692840	Antioxidant defense
SOD3	rs1799895 (R213G)	4:24407643	Antioxidant defense
TF	rs3811647	3:133748654	Iron handling
TFAM	rs1937 (S12T)	10:58385967	Mitochondrial biogenesis
TMPRSS6	rs855791 (V736A)	22:37072479	Iron handling
TPH2	rs4570625 (-703G/T)	12:71939032	Brain / neuromuscular
VEGFA	rs2010963 (-634G/C)	6:43770613	Cardiovascular / VEGF
VEGFA	rs699947 (-2578C/A)	6:43768652	Cardiovascular / VEGF

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This document does not contain personal genotype data, medication or supplement regimens, or individualized clinical recommendations. Variant interpretations reflect the published literature as of the document date and may be revised as new evidence accumulates.