# Mitochondrial Genetic Pathway Reference

## Mitochondrial Genetic Pathway Reference

*Biogenesis, OXPHOS, Antioxidant Defense, NAD+ Metabolism, Sirtuins, Dynamics, Mitophagy, mtDNA*

10 Functional Categories • ~67 Single-SNP Variants Catalogued • 21 Region-Scan Loci

*Educational reference document | No personal genotype data*

## 1. Purpose and Scope

This document is a standalone educational reference describing the biology of mitochondrial regulation in humans, the genes that govern mitochondrial biogenesis, the oxidative phosphorylation (OXPHOS) machinery, $NAD^+$ metabolism and the sirtuins, mitochondrial coenzyme $Q_{10}$ biosynthesis and recycling, the proton-leak / uncoupling system, the antioxidant response (NRF2/KEAP1 axis, SOD2, GPX1, CAT), mitochondrial dynamics (fusion, fission), mitophagy and quality control (PINK1/Parkin/PARK7), and the mitochondrial genome itself (POLG, TFAM, mtDNA haplogroups). For each gene, the well-studied common and rare variants are catalogued with their functional consequence, cofactor or substrate dependencies, and the supplement, dietary, behavioral, or pharmacologic targets that map to each pathway node. 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, OMIM, ClinVar, PharmGKB, and meta-analyses through 2026. Sources include Nature, Nature Genetics, Nature Communications, Cell, Cell Metabolism, Science, PNAS, Diabetes, Diabetologia, NEJM, Aging Cell, GeroScience, J Clin Invest, FASEB J, Antioxidants, Free Radical Biology & Medicine, the GWAS Catalog, and the dbSNP / OMIM / ClinVar databases. The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations.

Mitochondrial biology is highly polygenic and pleiotropic. Most common variants catalogued here confer small individual effects (per-allele changes of a few percent in enzyme activity, or odds ratios of 1.10–1.50 for binary outcomes); clinical significance arises from cumulative patterns and gene–environment interactions. A small number of rare, large-effect variants — PINK1, PRKN, PARK7 (recessive juvenile parkinsonism); POLG (Alpers, ataxia-neuropathy, PEO); MFN2 (Charcot-Marie-Tooth 2A); OPA1 (autosomal dominant optic atrophy); and the mtDNA mutations m.3243A>G (MELAS) and m.11778G>A / m.3460G>A / m.14484T>C (LHON) — produce dramatic phenotypes when present and are included for completeness even when their population frequency is below 1%. Heritability of mtDNA copy number is approximately 0.30–0.60 (Curran et al., Twin Res Hum Genet 2007); skeletal-muscle respiratory capacity $h^2 \approx 0.5$ (Bouchard 1999); $VO_2$max trainability $h^2 \approx 0.47$ (HERITAGE Family Study, Bouchard 2011 J Appl Physiol).

# 2. Pathway Biology

## 2.1 Mitochondrion architecture and primary functions

Mitochondria are double-membrane organelles descended from an α-proteobacterial endosymbiont. The outer membrane is permeable to small molecules (≤ 5 kDa) through VDAC porins; the inner membrane is highly impermeable, electrochemically polarized (ΔΨm ≈ −150 to −180 mV inside-negative), and convoluted into cristae that house the respiratory chain. The matrix contains the mtDNA, the TCA-cycle and β-oxidation enzymes, the pyruvate dehydrogenase complex, and most of the proteins of mitochondrial protein synthesis. Mitochondria are the dominant site of ATP production through OXPHOS, the dominant intracellular generator of reactive oxygen species (ROS), a central calcium store, the gatekeeper of intrinsic apoptosis through cytochrome c release and the mitochondrial permeability transition pore, and a metabolic-signaling hub through the $NAD^+$/NADH ratio, acetyl-CoA, succinate, fumarate, and α-ketoglutarate.

## 2.2 Oxidative phosphorylation

The electron transport chain (ETC) consists of four enzyme complexes (I–IV) and two mobile electron carriers (coenzyme $Q_{10}$ and cytochrome c) that pump protons across the inner membrane to generate the proton-motive force. Complex V (ATP synthase) uses the proton-motive force to phosphorylate ADP. Complex I (NADH:ubiquinone oxidoreductase, ~45 subunits, 7 mtDNA-encoded ND subunits + ~38 nuclear-encoded NDUF subunits) accepts electrons from NADH and transfers them through FMN and 8 Fe-S clusters to ubiquinone, pumping 4 $H^+$ per NADH. Complex II (succinate dehydrogenase, 4 subunits SDHA–D, all nuclear-encoded) is the only ETC complex without proton pumping; it links the TCA cycle to the ETC by oxidizing succinate to fumarate and reducing ubiquinone. Complex III (cytochrome $bc_1$ complex, 11 subunits, 1 mtDNA-encoded MT-CYB) shuttles electrons from $CoQH_2$ to cytochrome c via the Q-cycle, pumping 4 $H^+$ per electron pair. Complex IV (cytochrome c oxidase, 14 subunits, 3 mtDNA-encoded MT-CO1–3) is the terminal oxidase, transferring 4 electrons to $O_2$ to form 2 $H_2O$, pumping 2 $H^+$ per electron pair. Complex V ($F_1F_0$-ATP synthase, ~17 subunits, 2 mtDNA-encoded MT-ATP6/8) couples proton flux back into the matrix to ATP synthesis. Theoretical maximum yield: 2.5 ATP per NADH and 1.5 ATP per $FADH_2$.

## 2.3 Mitochondrial biogenesis and the PGC-1α hub

PGC-1α (encoded by PPARGC1A) is the master coactivator of mitochondrial biogenesis (Spiegelman 1998 Cell; Wu 1999 Cell). It is regulated post-translationally by AMPK (activates by phosphorylation, in response to energy stress and exercise), SIRT1 (activates by deacetylation, in response to high $NAD^+$), and CLK2 / GSK3β (inactivate by phosphorylation). PGC-1α coactivates several transcription factors: NRF1 and NRF2 (also called GABPA, distinct from the antioxidant NRF2 / NFE2L2), which drive transcription of nuclear-encoded mitochondrial genes including TFAM; ERRα, ERRγ (estrogen-related receptors); PPARα, PPARδ, PPARγ (fatty-acid oxidation, lipogenesis); FOXO1; YY1. TFAM, once translated, is imported into the mitochondrial matrix where it activates mtDNA transcription and stabilizes mtDNA — it determines mtDNA copy number. PGC-1β (PPARGC1B) and PRC have overlapping functions. PGC-1α expression is induced by exercise, cold exposure, fasting, polyphenols (resveratrol via SIRT1, pterostilbene), and β-adrenergic signaling; it is suppressed by chronic insulin/mTORC1 signaling.

## 2.4 $NAD^+$ metabolism, sirtuins, and PARPs

$NAD^+$ is the central redox cofactor and the obligate cosubstrate of the seven sirtuins (SIRT1–7), the PARPs (poly-ADP-ribose polymerases), and CD38/CD157 (cyclic ADP-ribose hydrolases). Cellular $NAD^+$ is generated through three pathways. The de novo pathway from tryptophan via the kynurenine route is operative mainly in liver and kidney. The Preiss–Handler pathway converts nicotinic acid to $NAD^+$ through NAPRT and NMNAT. The salvage pathway, accounting for ≈85% of cellular $NAD^+$, recycles nicotinamide (NAM) through NAMPT (rate-limiting; salvage is the dominant route in skeletal muscle, brain, and immune cells) to NMN, then to $NAD^+$ through NMNAT1/2/3. Nicotinamide riboside (NR), the supplemental $NAD^+$ precursor, is phosphorylated by NMRK1 (ubiquitous) or NMRK2 (skeletal-muscle-specific). $NAD^+$ levels decline 30–50% across most tissues by the seventh decade (Massudi 2012 PLoS One; Yoshino 2018 Cell Metab). The major drivers of $NAD^+$ decline are reduced NAMPT expression and increased $NAD^+$ consumption by inflammation-induced CD38 (Camacho-Pereira 2016 Cell Metab) and PARP1 (DNA-damage-driven).

Mitochondrial sirtuins are SIRT3 (the dominant deacetylase, regulating SOD2, IDH2, LCAD, HMGCS2, complex I subunit NDUFA9, complex II subunit SDHA), SIRT4 (lipoamidase and ADP-ribosyltransferase activities; suppresses pyruvate dehydrogenase and glutamate dehydrogenase under nutrient sufficiency), and SIRT5 (deacylase for succinyl-, malonyl-, glutaryl-lysine marks). SIRT3 expression rises under caloric restriction, fasting, and exercise (Ahn 2008 PNAS); knockout mice show elevated mitochondrial protein acetylation, increased ROS, and accelerated age-related pathology.

## 2.5 Mitochondrial reactive oxygen species and antioxidant defense

Approximately 0.1–1% of electrons in the ETC “leak” directly to molecular oxygen, producing superoxide ($O_2^{\bullet-}$) primarily at Complex I (matrix-side) and Complex III (both matrix and intermembrane space sides). Superoxide is the dominant primary mitochondrial ROS; secondary ROS include $H_2O_2$, hydroxyl radical (•OH, via Fenton chemistry with $Fe^{2+}$), and peroxynitrite ($ONOO^-$, via reaction with NO). Mitochondrial defense is layered: (1) SOD2 (MnSOD, matrix) and SOD1 (Cu/ZnSOD, intermembrane space) dismutate $O_2^{\bullet-}$ to $H_2O_2$; (2) GPX1 and GPX4 (glutathione peroxidases, GSH-dependent), CAT (catalase, peroxisomal/cytosolic), peroxiredoxins (PRDX3/5 mitochondrial, thioredoxin-dependent) clear $H_2O_2$ to $H_2O$; (3) GSH/GSSG ratio is maintained by glutathione reductase (NADPH-dependent); (4) thioredoxin/thioredoxin reductase 2 (TXN2/TXNRD2) mitochondrial system. The transcriptional master regulator of ≥ 200 antioxidant and detoxification genes is NRF2 (encoded by NFE2L2). Under basal conditions NRF2 is bound to KEAP1 and ubiquitinated by Cullin-3; oxidative or electrophilic modification of KEAP1 cysteines (C151, C273, C288) releases NRF2, which translocates to the nucleus, dimerizes with small Maf proteins, and binds antioxidant response elements (AREs) (Kensler 2007 Annu Rev Pharmacol Toxicol; Hayes & Dinkova-Kostova 2014 Trends Biochem Sci). NRF2 induces SOD1, NQO1, HMOX1 (heme oxygenase-1), GCLC and GCLM (γ-glutamylcysteine ligase, glutathione synthesis), GSTs, TXNRD1, and many more. Pharmacologic NRF2 activators include sulforaphane (from broccoli sprouts via myrosinase), curcumin, R-α-lipoic acid, dimethyl fumarate, and bardoxolone methyl.

## 2.6 Mitochondrial dynamics: fusion and fission

Mitochondria continuously fuse and divide. Outer-membrane fusion is mediated by mitofusins MFN1 and MFN2 (large GTPases, antiparallel HR1 dimers across opposing membranes); inner-membrane fusion is mediated by OPA1 (a dynamin-like GTPase whose long L-OPA1 and short S-OPA1 forms generated by OMA1 and YME1L proteolysis collaborate to fuse inner

membranes and reorganize cristae). Fission is mediated by DRP1 (DNM1L), a cytosolic GTPase recruited to the outer membrane by adaptors MFF, FIS1, MID49, and MID51; the endoplasmic reticulum marks fission sites. Phosphorylation of DRP1 at Ser616 (by CDK1, ERK1/2, CaMKII) drives fission; phosphorylation at Ser637 (by PKA) inhibits fission and promotes elongation. The fusion–fission balance determines mitochondrial morphology and function: fusion (and elongation) promotes content mixing and complementation of damaged mtDNA, supports oxidative metabolism, and resists apoptosis; fission produces small mitochondria suitable for transport, segregates damaged content for mitophagy, and facilitates apoptosis. Loss-of-function variants in MFN2 cause Charcot-Marie-Tooth type 2A; OPA1 LoF causes autosomal dominant optic atrophy; DRP1 LoF causes encephalopathy with refractory epilepsy.

## 2.7 Mitophagy and mitochondrial quality control

Damaged mitochondria are cleared by selective autophagy (mitophagy). Two pathways dominate. (1) The PINK1–Parkin pathway (Pickrell & Youle 2015 Neuron): in healthy mitochondria PINK1 is constitutively imported and cleaved by PARL; on a depolarized mitochondrion PINK1 import fails, PINK1 stabilizes on the outer membrane, dimerizes, and phosphorylates ubiquitin (Ser65) and Parkin's UBL domain. Activated Parkin (an E3 ligase) ubiquitinates outer-membrane proteins (Mfn1/2, MIRO, VDAC); phospho-ubiquitin is bound by the autophagy receptors OPTN, NDP52, TAX1BP1, NBR1, p62, which recruit LC3-positive autophagosomes. PARK7 (DJ-1) is recruited downstream of PINK1/Parkin to depolarized mitochondria and supports OPTN recruitment (Cornelissen 2020 J Cell Biol). Loss of PINK1, PRKN, or PARK7 causes autosomal recessive early-onset Parkinson's disease. (2) Receptor-mediated mitophagy: BNIP3, BNIP3L (NIX), FUNDC1 each contain LIR motifs that bind LC3 directly without requiring ubiquitination; this pathway dominates under hypoxia, erythrocyte maturation, and developmentally programmed mitochondrial loss. Pharmacologic mitophagy inducers include urolithin A (Ryu 2016 Nat Med; D'Amico 2021 Cell Reports Med), spermidine (Eisenberg 2009 Nat Cell Biol), and rapamycin (mTORC1 inhibition, indirect).

## 2.8 mtDNA: structure, replication, and inheritance

Human mtDNA is a 16,569 bp circular molecule encoding 13 OXPHOS subunits (7 in Complex I: ND1–6, ND4L; 1 in Complex III: CYB; 3 in Complex IV: CO1–3; 2 in Complex V: ATP6, ATP8), 22 tRNAs, and 2 rRNAs. Each cell carries 100–10,000 mtDNA copies (heart and muscle highest; mtDNA copy number $h^2 \approx 0.30–0.60$, Curran 2007 Twin Res Hum Genet). mtDNA is replicated by DNA polymerase γ (POLG catalytic subunit, POLG2 accessory subunit) in collaboration with TWNK helicase (Twinkle) and SSBP1. Pathogenic POLG variants (over 300 reported, OMIM 174763) cause progressive external ophthalmoplegia (PEO), ataxia-neuropathy syndromes, Alpers-Huttenlocher syndrome, and mitochondrial neurogastrointestinal encephalopathy (MNGIE phenocopy). Carriers should avoid valproate (associated with fatal hepatotoxicity in POLG mutation carriers), and certain antivirals (d4T, ddI, AZT) that inhibit POLG. mtDNA is maternally inherited. Heteroplasmy (mixed wild-type and mutant mtDNA within a single cell) determines clinical penetrance for pathogenic mtDNA mutations — a threshold (typically 60–90%) must be exceeded for biochemical and clinical effect (Wallace 2018 Nat Rev Genet).

## 2.9 mtDNA haplogroups and mitonuclear interactions

Common combinations of linked mtDNA SNPs define population-level haplogroups. European haplogroups H, V, U, K, J, T, I, W, X. African L0–L3. Asian M, N, A, B, C, D, F. Haplogroup H

(~40–50% of Europeans) is associated with the most efficient OXPHOS coupling (Gómez-Durán 2010 Hum Mol Genet). Haplogroup J (defined by m.4216T>C in MT-ND1 and m.13708G>A in MT-ND5) shows mildly reduced Complex I activity, lower ATP, and lower ROS — the basis for the “uncoupling-to-survive” hypothesis (Wallace 2005 Cold Spring Harb Symp). Haplogroup J is increased in centenarians from Northern Italy (De Benedictis 1999 FASEB J), Ireland (Ross 2001 Exp Gerontol), and Finland (Niemi 2005 Hum Hered) but not Southern Italy (Dato 2004 Eur J Hum Genet) or Spain (Garatachea 2011 Age). Haplogroup J amplifies penetrance of LHON-causing m.11778G>A, m.3460G>A, m.14484T>C primary mutations (Brown 2002 Am J Hum Genet; Hudson 2007 Brain). Haplogroup K and its subclade K2 (with m.T9716C) show reduced all-cause and cardiac mortality (Raule 2014 Aging Cell; Schulze 2018 bioRxiv). Mitonuclear compatibility — the alignment between nuclear-encoded and mtDNA-encoded ETC subunits — is increasingly recognized as a determinant of metabolic flexibility and lifespan (Mossman 2019 Mol Biol Evol).

### 2.10 Cross-talk with metabolic, cardiovascular, and neurodegenerative biology

Mitochondrial biology connects to virtually every aging-relevant pathway. Mitochondrial dysfunction is one of the canonical hallmarks of aging (López-Otín 2013, 2023 Cell). Skeletal-muscle mitochondrial capacity correlates with $VO_2$max, insulin sensitivity, and physical function in older adults; PGC-1α–driven biogenesis underlies most of the benefits of aerobic exercise (Holloszy 1967 J Biol Chem; Booth 2012 Compr Physiol). Pancreatic β-cell mitochondrial dysfunction is central to type-2-diabetes pathogenesis. Cardiac mitochondrial dysfunction underlies most heart failure with preserved ejection fraction. Substantia nigra dopaminergic neurons have very high basal mitochondrial activity and are uniquely vulnerable to mitophagy failure (Parkinson's disease). Glymphatic clearance of Aβ and tau peptides is sleep-stage-dependent and bioenergetically demanding (Xie 2013 Science). Mitochondrial calcium uptake through the MCU complex couples metabolic demand to ATP supply. Almost every validated lifespan-extending intervention — caloric restriction, exercise, rapamycin, metformin, $NAD^+$ precursors, urolithin A, spermidine — converges on mitochondrial biogenesis or quality control.

## 3. Functional Categories: Genes, Variants, and Cofactors

### 3.1 Mitochondrial biogenesis — transcriptional coactivators and factors

PGC-1α (PPARGC1A) is the central coactivator. It interacts with NRF1, NRF2/GABPA, ERRα, PPARs, and YY1 to drive nuclear transcription of >1,000 mitochondrial-related genes. NRF1 transcribes TFAM, which then translocates to mitochondria and licenses mtDNA replication. Variants in this category primarily affect inducible (exercise-, cold-, fasting-driven) mitochondrial biogenesis.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **PPARGC1A** | rs8192678 (Gly482Ser, c.1444G>A, c.1564G>A) | Coding missense; A allele (Ser482) reduces PPARGC1A mRNA in muscle and islets ~30%; faster PGC-1α protein degradation; | *Ling 2004 Diabetes; Stadler/Brunmair 2023 Diabetologia* | A (Ser) → endurance |

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| | | CRISPR-Cas9 isogenic study confirmed C→T allele alters adipocyte differentiation, lipogenesis, and PGC-1α turnover | *(PMC10244287); Vimaleswaran 2008 PLoS One meta-analysis* | underperformance, T2D OR ~1.13, NAFLD susceptibility; MAF A ~0.36 EUR |
| **PPARGC1A** | rs7665116 (intronic) | Modifier of Huntington's disease age of onset; reflects PPARGC1A regulatory function | *Weydt 2009 Cell Metab* | Modifier locus, modest |
| **PPARGC1A** | rs3856806 (Thr528Thr, syn) | Synonymous coding variant; tag SNP for PPARGC1A haplotypes; obesity / T2D associations in some cohorts | *Vimaleswaran 2008* | Modest, mixed |
| **PPARGC1A** | rs2970847 (Thr394Thr, syn) | Synonymous tag SNP; weak T2D and obesity signals | *Esterbauer 2002 J Mol Med* | Modest |
| **NRF1** | rs6949152 (intronic, A>G) | Intronic regulatory variant; A/A genotype associated with higher MHC-I (slow-twitch) fiber proportion in women; HD age-of-onset modifier | *Yvert 2020 Genes (PMC7563119); Weydt 2009; Garatachea 2014 RICYDE* | A allele → slow-twitch direction in women; modifier in HD |
| **NRF1** | rs7781972, rs1882094, rs3735006 | Tag and non-synonymous variants; modifier loci in HD | *Weydt 2009 Cell Metab* | Modifier |
| **TFAM** | rs1937 (G>C, S12T) | Coding missense; C allele (Thr12) replaces serine in mitochondrial targeting sequence; longevity association in CLHLS Chinese cohort (n=3,294, p=0.003) | *Zhao 2021 BMC Geriatr (PMC8722189); Garatachea 2014 RICYDE* | C/G genotype → longevity OR ~1.18 in Chinese; replication mixed in Europea |

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| | | | | ns |
| **TFAM** | rs2306604 (intronic) | Intronic; TFAM expression and mtDNA copy number; AD-risk modifier in some studies | *Belin 2007 Brain* | Modest |
| **ESRRA** | rs3217060 (23-bp microsatellite) | Promoter microsatellite; modifier of HD onset | *Weydt 2009 Cell Metab* | Modifier |
| **MFN2** | rs3753579 (promoter) | Promoter; modifier of HD onset | *Weydt 2009* | Modifier |

*Cofactors: PGC-1α phosphorylation requires AMP/ADP-activated AMPK and ATP; PGC-1α deacetylation requires SIRT1 and $NAD^+$. NRF1 and TFAM transcription factors require zinc (NRF1 zinc finger). TFAM mtDNA binding does not require $Mg^{2+}$ but mtDNA replication by POLG is $Mg^{2+}$-dependent. Practical levers: aerobic exercise (induces PGC-1α within hours), resistance training, cold exposure, fasting / caloric restriction, ketogenic state, $NAD^+$ precursors (raise SIRT1 substrate), polyphenols (resveratrol, pterostilbene activate SIRT1), β-adrenergic stimulation (cold).*

## 3.2 $NAD^+$ supply — substrate availability for sirtuins, PARPs, and the ETC

$NAD^+$ is the central redox cofactor and the obligate cosubstrate of sirtuins. Tissue $NAD^+$ declines with age, driving multiple downstream defects.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **NAMPT** | rs1319501 (-948G>T, promoter) | Promoter variant; T allele reduces NAMPT transcription; lower plasma visfatin/eNAMPT | *Bailey 2006 J Clin Endocrinol Metab; Garten 2025 review* | T → lower NAMPT; modest evidence |
| **NAMPT** | rs2058539, rs10487819 | Promoter and intronic tag SNPs; metabolic-syndrome and T2D signals | *Bailey 2006; Zhang 2011* | Modest |
| **NMRK1** | Coding region | NR → NMN kinase; ubiquitously expressed; rare functional variants only | *Ratajczak 2016 Nat Commun* | Rare LoF only |
| **NMRK2** | Coding (skeletal-muscle isoform) | Skeletal-muscle NR→NMN kinase; relevant for NR pharmacology in muscle | *Ratajczak 2016 Nat Commun* | Pharmacology-relevant |

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **NADSYN1** | rs12785878 (intronic) | Primarily a 25-OH-vitamin-D level locus; D-NAD axis crosstalk | *Wang 2010 Lancet* | Pleiotropic |
| **CD38** | rs1130169 | Major $NAD^+$-consuming enzyme; CD38 expression rises with age and inflammation, depleting $NAD^+$; CD38 inhibition by apigenin/quercetin raises $NAD^+$ in mice | *Camacho-Pereira 2016 Cell Metab* | Functional locus |

*Cofactors: NAMPT requires PRPP and ATP. NMRK1/2 require ATP. NMNAT1/2/3 require ATP. CD38 hydrolyzes $NAD^+$; pharmacologic CD38 inhibitors are flavonoids (apigenin, quercetin). Practical levers: NR (300–1000 mg/day) or NMN supplementation; niacin/nicotinamide (lower priority); exercise (induces NAMPT, suppresses CD38); fasting; CD38 inhibitor flavonoids.*

## 3.3 Sirtuin regulation — $NAD^+$-dependent deacylases

SIRT3 is the dominant mitochondrial deacetylase, regulating SOD2, IDH2, LCAD, HMGCS2, complex I subunit NDUFA9, and complex II subunit SDHA. SIRT4 has lipoamidase and ADP-ribosyltransferase activities. SIRT5 deacylates succinyl/malonyl/glutaryl-lysine marks. FOXO3 is a downstream effector with strong longevity associations across multiple human populations.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **SIRT3** | rs11555236 (intronic) | Intronic; longitudinal mortality association in Treviso Longeva (Italian elderly) | *Albani 2014 Age PMC; Treviso Longeva* | Minor allele → longevity in Italian cohort |
| **SIRT3** | rs3782116 (VNTR-adjacent enhancer) | Long-allele intronic VNTR-adjacent variant; associated with male centenarians in Italy; not replicated in French cohort | *Bellizzi 2005 Genomics; Lescai 2009 Eur J Hum Genet* | Population-specific |
| **SIRT3** | rs939915 | Tag SNP; meta-analysis positive longevity association | *Wei 2017 Oncotarget* | Positive in meta-analysis |
| **SIRT3** | rs3825075, rs4980329, rs511744, rs7934919, rs1045288, rs559422, rs3817630, rs2293168 | Tag SNPs across SIRT3 locus; tested in centenarian cohorts; mixed results across populations | *Lescai 2009 Eur J Hum Genet* | Mixed evidence |

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **FOXO3** | rs2802292 (intronic, T>G) | G allele creates a HSF1-binding site in an intronic enhancer; under stress (oxidative, low glucose) HSF1 binds and induces FOXO3 transcription; G/G associated with 1.9-fold higher odds of reaching 95+ in HALE/Okinawan cohort, replicated in 11+ populations; G allele associated with longer telomeres and higher telomerase activity | *Donlon 2018 Aging Cell PMC6009585; Willcox 2008 PNAS; Chen 2024 npj Aging* | G = longevity allele; T = non-longevity (risk); MAF G ~0.25 EUR |
| **FOXO3** | rs13217795, rs2253310, rs2764264, rs9400239, rs4946935 | Intronic FOXO3 variants in high LD with rs2802292; longevity associations replicated in Japanese, Italian, Chinese, German cohorts | *Anselmi 2009 Rejuv Res; Flachsbart 2009 PNAS; Li 2009 Hum Mol Genet* | Same haplotype block |

*Cofactors: All sirtuins require $NAD^+$ as obligate cosubstrate (consumed stoichiometrically per deacetylation). SIRT3 mitochondrial activity is also driven by exercise and CR. Practical levers: $NAD^+$ precursors (NR, NMN); polyphenol-mediated SIRT1 activators (resveratrol, pterostilbene); exercise; fasting / IF / CR; ketogenic state.*

## 3.4 OXPHOS machinery — Complexes I–V

Common nuclear-encoded variants in OXPHOS subunits are largely well-tolerated. Rare loss-of-function variants cause Mendelian mitochondrial disease (Leigh syndrome, MELAS, LHON). For this reference, we catalog the commonly studied tag SNPs and mark the canonical Mendelian loci.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **NDUFS7, NDUFS8, NDUFA13** | Rare LoF (e.g. NDUFS7 c.16C>T, p.Arg6Trp) | Complex I structural subunits; rare biallelic LoF causes Leigh syndrome (OMIM 256000) | *Triepels 1999 J Clin Invest; OMIM* | Mendelian, recessive |
| **SDHA, SDHB, SDHC, SDHD** | Rare LoF (heterozygous and biallelic) | Complex II / paraganglioma–pheochromocytoma syndromes; tumor-suppressor function (heterozygous LoF predisposes to PGL/PCC) | *Astuti 2001 Am J Hum Genet; OMIM 185470, 115310, 605373, 168000* | PGL/PCC tumor predisposition |
| **SDHA** | rs6555055 (intronic) | Modest GWAS signals for body composition | *GWAS Catalog* | Modest |
| **CYC1, MT-CYB** | Rare and common | Complex III subunits | *OMIM* | Mostly rare |

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| | variants | | | |
| **MT-ND1, MT-ND4, MT-ND6** | m.3460G>A, m.11778G>A, m.14484T>C — the three primary LHON mutations | Complex I subunits; cause Leber's hereditary optic neuropathy (LHON, OMIM 535000); penetrance amplified by haplogroup J background and by male sex; ~50% males / ~10% females penetrance | *Wallace 1988 Science; Brown 2002 Am J Hum Genet; Hudson 2007 Brain* | Pathogenic mtDNA |
| **MT-TL1** | m.3243A>G (MELAS) | tRNA-Leu(UUR); causes MELAS (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes); maternally inherited diabetes and deafness (MIDD) at lower heteroplasmy | *Goto 1990 Nature* | Pathogenic mtDNA |
| **MT-CO1, CO2, CO3** | Common haplogroup-defining SNPs and rare LoF | Complex IV subunits; haplogroup background | *Wallace 2018 Nat Rev Genet* | Common haplogroup signal |
| **MT-ATP6, MT-ATP8** | m.8993T>G (NARP); m.8993T>C (Leigh) | Complex V subunits; cause neuropathy ataxia retinitis pigmentosa and Leigh syndrome at high heteroplasmy | *Holt 1990 Am J Hum Genet* | Pathogenic mtDNA |

*Cofactors: Complex I requires FMN (from riboflavin) and 8 Fe-S clusters. Complex II requires FAD (from riboflavin) and 3 Fe-S clusters. Complex III requires heme (Fe-protoporphyrin IX) and the 2Fe-2S Rieske cluster. Complex IV requires heme a/a3 and 2 Cu sites. Complex V requires ADP, Pi, and the proton motive force. Practical levers: B2 (riboflavin) sufficiency for FMN/FAD; iron sufficiency for Fe-S clusters and heme; copper sufficiency for COX (Complex IV); selenium sufficiency for selenocysteine-containing proteins; sulfur amino acid pool (cysteine/methionine via NAC, taurine) for Fe-S biogenesis.*

## 3.5 Coenzyme $Q_{10}$ biosynthesis and recycling

$CoQ_{10}$ (ubiquinone) shuttles electrons from Complexes I and II to Complex III and is also the dominant lipid-soluble antioxidant in extramitochondrial membranes. Endogenous synthesis declines with age; statins suppress synthesis upstream by inhibiting HMG-CoA reductase (mevalonate pathway).

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **NQO1** | rs1800566 (P187S, c.559C>T) | Coding missense; T allele (Ser187) produces an unstable protein rapidly degraded by the | *Siegel 2001 Cancer Res; Fischer 2011* | T (Ser) = LoF; risk for |

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| | | proteasome; T/T genotype has no NQO1 protein or activity; recycles ubiquinone to ubiquinol; PolyPhen 'possibly damaging' | *BMC Res Notes (PMC3160390); ClinVar (Pathogenic, drug-response)* | impaired CoQ recycling, drug toxicity, breast/lung/colorectal cancer; MAF T ~0.20 EUR, ~0.45 ASN |
| **NQO2** | rs1143684 (L47F) | Coding missense; L→F substitution; weaker functional evidence than NQO1 P187S | *Fischer 2011 BMC Res Notes* | Modest |
| **COQ2** | rs6818847 | CoQ biosynthesis enzyme (4-hydroxybenzoate octaprenyltransferase); MSA risk and statin myopathy susceptibility | *Mitsui 2013 NEJM (MSA); Oh 2013 (statin myopathy)* | MSA risk; myopathy |
| **COQ2** | Rare LoF | Primary $CoQ_{10}$ deficiency, autosomal recessive (OMIM 614652); responsive to high-dose $CoQ_{10}$ supplementation | *Quinzii 2006 Am J Hum Genet* | Mendelian |
| **COQ6** | rs8500 (M406V) | CoQ biosynthesis (5-demethoxyubiquinone-6 hydroxylase); rare LoF causes nephrotic syndrome with sensorineural deafness | *Heeringa 2011 J Clin Invest; Fischer 2011 (modest common-variant)* | Mostly rare |
| **COQ3** | rs6925344 (G272S) | CoQ biosynthesis (3-demethylubiquinone-9 3-O-methyltransferase); modest CoQ-status effects in pilot study | *Fischer 2011 BMC Res Notes* | Modest |
| **COQ7** | rs11074359 (M103T) | CoQ biosynthesis (5-demethoxyubiquinone hydroxylase); modest evidence; rare LoF causes severe encephalopathy | *Fischer 2011; Freyer 2015 J Med Genet* | Modest |
| **PDSS1, PDSS2** | Rare LoF | Prenyl-side-chain assembly; primary $CoQ_{10}$ deficiency | *Mollet 2007 Am J Hum Genet* | Mendelian |

*Cofactors: $CoQ_{10}$ biosynthesis from tyrosine via HMG-CoA reductase→ mevalonate → farnesyl-PP → decaprenyl-PP, joined to 4-hydroxybenzoate; requires B6 (P5P, for tyrosine), B2 (FAD),*

*B3 ($NAD^+$), vitamin C, folate, methionine (for SAM-dependent methylations by COQ3 and COQ5). NQO1 catalyzes ubiquinone→ubiquinol using NAD(P)H. Practical levers: ubiquinol form preferred over ubiquinone in NQO1 P187S T-allele carriers and statin users (bypasses NQO1 dependence); typical doses 100–200 mg/day; statin users may need 100–300 mg/day; co-administration with fat for absorption.*

## 3.6 Proton leak and uncoupling

Mild uncoupling reduces ROS production at the cost of ATP-synthesis efficiency — the "uncoupling-to-survive" hypothesis. UCP2 is broadly expressed; UCP3 is largely restricted to skeletal muscle and heart.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **UCP2** | rs659366 (-866G>A, promoter) | Promoter variant in transcription-factor binding region; A allele increases UCP2 transcription in some contexts (oxidative stress) but decreases in HUVECs under high glucose — context-dependent; A allele → increased premature CAD risk (recessive OR 1.43); G allele beneficial in haplotype longevity analysis | *Esterbauer 2001 Nat Genet; Vargas-Alarcón 2018 Lipids Health Dis (PMC6082227); Rose 2011 PLoS One PMC (uncoupling-to-survive); Zheng 2019 Endocrine* | A allele context-dependent; G allele longevity |
| **UCP2** | rs660339 (Ala55Val, c.164C>T) | Coding missense; T/T (Val/Val) associated with higher visceral abdominal fat, metabolic-syndrome traits; modest BMI effects in meta-analysis | *Vargas-Alarcón 2018; Qian 2013 (meta-analysis)* | T/T → visceral fat; modest |
| **UCP3** | rs1800849 (-55C>T, promoter) | Promoter variant; T allele showed favorable longevity haplotype in Italian cohort; T/T also associated with higher visceral fat | *Rose 2011 PLoS One; Vargas-Alarcón 2018* | T allele has mixed effects |
| **UCP1** | rs1800592 (-3826A>G, promoter) | Promoter variant; G allele reduces UCP1 expression in BAT; modest BMI association | *Heilbronn 2000 J Mol Med* | Modest BMI |
| **SLC25A4 (ANT1)** | Rare LoF | Adenine nucleotide translocator; rare LoF causes adPEO and cardiomyopathy | *Kaukonen 2000 Science* | Mendelian |

*Cofactors: UCP2 and UCP3 activity depends on free fatty acids (activator) and purine nucleotides (GDP, GTP, ATP, ADP — inhibitors). Reactive lipid species (4-HNE) activate UCP2/3. Levers: thermogenic stimuli (cold exposure, brown-fat activation); polyunsaturated fats; exercise.*

## 3.7 ROS generation, sensing, and antioxidant defense

This is the most clinically actionable category. Mitochondrial superoxide is dismutated by SOD2 to $H_2O_2$, which is then cleared by GPX1 (GSH-dependent), CAT, peroxiredoxins (PRDX3/5), and the thioredoxin system (TXN2/TXNRD2). Transcription is centrally regulated by NRF2 (NFE2L2) acting at antioxidant response elements (AREs) and held in check by KEAP1 under non-stress conditions.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **SOD2** | rs4880 (V16A, c.47T>C; aka A16V; on minus-strand gene reported as A>G on dbSNP forward) | Coding missense in mitochondrial targeting sequence; A allele (Ala16) preserves α-helical MTS structure favorable for mitochondrial import; T allele (Val16) disrupts MTS α-helix; Ala variant has 30–40% higher MnSOD mitochondrial activity | *Sutton 2003 Pharmacogenetics; Bastaki 2006 Pharmacogenomics J; Broz 2022 Antioxidants (PMC9774195); Khani 2025 J Kermanshah Univ Med Sci (PMC); Möllsten 2009 Diabetologia* | T (Val) = risk for low MnSOD activity → oxidative stress; T1D nephropathy OR 1.45; OSA severity; depression risk; MAF T ~0.45 EUR |
| **SOD2** | rs2855116, rs5746136 | Intronic and 3'-region tag SNPs in LD with rs4880 | *Möllsten 2009 Diabetologia* | LD with rs4880 |
| **GPX1** | rs1050450 (P198L, c.593C>T) | Coding missense; T allele (Leu198) reduces GPX1 enzyme activity in response to selenium; T allele → cardiovascular events in CHD | *Forsberg 2000 Free Radic Biol Med; Hamanishi 2004 Diabetes* | T (Leu) = risk for reduced enzyme; selenium-rescuable |
| **CAT** | rs1001179 (-262C>T, promoter) | Promoter variant; T allele associated with lower erythrocyte catalase activity; CVD risk weak but consistent | *Forsberg 2001 BMC Genet; Forsblom 2011 Diabetologia* | T → lower CAT; risk |
| **CAT** | rs769214, rs769217 | Promoter and intronic variants; weaker signals | *Forsberg 2001* | Modest |
| **NFE2L2 (NRF2)** | rs6721961 (-617C>A, | Promoter variant in middle of ARE motif; A allele undermines NRF2 | *Marzec 2007 FASEB J; Wang* | A = risk; reduced |

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| | promoter) | self-induction (autoregulatory ARE binding); T2D risk (OR 1.56 in Chinese AA vs CC); impaired endothelial vasodilator response; vitiligo and lung function associations | *2015 Int J Mol Sci (PMC4519961); Marczak 2012 (PMC3599320); Shimoyama 2014 Pharmacogenet Genomics* | ARE self-induction; MAF A ~0.10 EUR, ~0.27 JPN |
| **NFE2L2** | rs35652124 (-274A>G, promoter) | Promoter variant; G allele reduces ARE binding affinity; CV mortality in dialysis; ALD susceptibility | *Shimoyama 2014; Shimoyama-Kishima 2019 Hepatol Commun (PMC6678089)* | G → reduced ARE binding |
| **NFE2L2** | rs2886162, rs1806649, rs7557529, rs2706110 | Tag SNPs across NFE2L2 locus | *Cordova 2018; Hartikainen 2012* | Modest tag SNPs |
| **KEAP1** | Rare somatic variants in cancer | Loss of NRF2 repression; constitutive NRF2 activation → chemoresistance in tumors; rare germline variants only | *Singh 2006 PLoS Med* | Rare germline; common somatic |
| **TXNRD2 (TXR2)** | rs5748469 (intronic) | Mitochondrial thioredoxin reductase; modest CV-disease signals | *Hellwege 2017 J Hum Genet* | Modest |
| **GSTP1** | rs1695 (Ile105Val) | Coding missense; Val105 reduces enzymatic activity towards electrophiles; conjugates GSH to xenobiotics; mixed cancer susceptibility evidence | *Garte 2001 Cancer Epidemiol Biomarkers Prev* | Val → reduced activity |
| **GSTM1, GSTT1** | Null deletions (CNV) | Whole-gene deletions (homozygous null) abolish enzyme activity; large copy-number polymorphisms; null alleles synergize with low antioxidant intake | *Garte 2001 Cancer Epidemiol Biomarkers Prev* | Null → reduced detox |

*Cofactors: SOD2 requires $Mn^{2+}$ (manganese sufficiency essential). GPX1 contains selenocysteine (selenium-dependent; activity is rescuable in P198L T-allele carriers with adequate Se intake — 100–200 µg/day target). CAT contains a heme group (iron-dependent). GSH synthesis requires cysteine (rate-limiting), glycine, and glutamate; γ-glutamylcysteine ligase (GCL = GCLC + GCLM) is the rate-limiting step. NRF2 activation triggers via electrophilic stress; pharmacologic activators include sulforaphane (broccoli sprouts via myrosinase), curcumin, R-α-lipoic acid, dimethyl fumarate. Practical levers: sulforaphane (broccoli sprouts → myrosinase → sulforaphane; or stabilized supplements like Avmacol); NAC or NACET (cysteine*

*donor for GSH); glycine; glutamine; selenium 100–200 µg; manganese sufficiency for SOD2; alpha-lipoic acid; curcumin (with pepperine for absorption).*

## 3.8 Mitochondrial dynamics — fusion and fission

Common functional polymorphisms in dynamics genes are sparse; most disease-relevant variants are rare, dominant-negative, or recessive Mendelian.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **MFN1** | Rare LoF | Outer-membrane fusion GTPase; rare LoF — most studies in mouse models | *Chen 2003 J Cell Biol* | Rare |
| **MFN2** | Rare missense (e.g. R94Q, V705I) | Outer-membrane fusion; mutations cause autosomal dominant Charcot-Marie-Tooth type 2A (CMT2A, OMIM 609260); also hereditary motor and sensory neuropathy with optic atrophy | *Züchner 2004 Nat Genet; OMIM 609260* | Mendelian, dominant |
| **MFN2** | rs3753579 (promoter) | HD age-of-onset modifier | *Weydt 2009 Cell Metab* | Modifier |
| **OPA1** | Rare LoF (~250 reported) | Inner-membrane fusion GTPase; haploinsufficiency causes autosomal dominant optic atrophy (DOA, OMIM 165500); some variants cause syndromic 'DOA-plus' | *Alexander 2000 Nat Genet; OMIM 165500* | Mendelian, dominant |
| **DNM1L (DRP1)** | Rare LoF/dominant-negative (e.g. A395D) | Cytosolic fission GTPase; dominant-negative mutations cause encephalopathy with refractory epilepsy and optic atrophy (OMIM 614388) | *Waterham 2007 NEJM; OMIM 614388* | Rare dominant |
| **MFF, FIS1, MID49, MID51** | Rare | DRP1 adaptors; rare LoF causes encephalopathy | *Koch 2016 J Med Genet* | Rare |

*Cofactors: Mfn1, Mfn2, OPA1, DRP1 are all GTPases requiring GTP hydrolysis. DRP1 phospho-Ser616 (CDK1, ERK1/2, CaMKII) drives fission; phospho-Ser637 (PKA) inhibits fission. Levers: exercise increases MFN2; cold exposure increases mitochondrial fission for thermogenesis; AMPK activation modulates DRP1 (metformin); pharmacologic Mdivi-1 inhibits DRP1 (research tool).*

## 3.9 Mitophagy and mitochondrial quality control

PINK1, Parkin, and DJ-1 (PARK7) form the central mitophagy axis; biallelic LoF in any of the three causes autosomal recessive early-onset Parkinson's disease.

| Gene | Variant / rsID | Functional consequence | Source | Risk / direction |
|---|---|---|---|---|
| **PINK1** | Rare LoF (homozygous or compound heterozygous) | Mitochondrial-targeted Ser/Thr kinase; phosphorylates ubiquitin and Parkin; biallelic LoF causes autosomal recessive early-onset PD (OMIM 605909); heterozygous carriers may have subclinical mitochondrial dysfunction | *Valente 2004 Science; OMIM 605909* | Recessive Mendelian (PD) |
| **PRKN (Parkin)** | Rare LoF, exon deletions/duplications | E3 ubiquitin ligase; ubiquitinates outer-membrane proteins on damaged mitochondria; biallelic LoF causes autosomal recessive juvenile Parkinson's disease (OMIM 600116); heterozygous carriers (~1–2% of population) have subtle striatal dysfunction | *Kitada 1998 Nature; OMIM 600116* | Recessive Mendelian (PD) |
| **PARK7 (DJ-1)** | Rare LoF | Oxidative-stress sensor; translocates to depolarized mitochondria, supports OPTN recruitment; biallelic LoF causes autosomal recessive PD (OMIM 606324) | *Bonifati 2003 Science; OMIM 606324* | Recessive Mendelian (PD) |
| **BNIP3, BNIP3L (NIX)** | Common SNPs limited evidence | Outer-membrane mitophagy receptors with LIR motifs; bind LC3 directly; dominant under hypoxia, erythrocyte maturation | *Sandoval 2008 Nature; Schweers 2007* | Limited common-variant data |
| **FUNDC1** | Rare LoF only | Hypoxia-induced mitophagy receptor on outer membrane | *Liu 2012 Nat Cell Biol* | Rare |

*Cofactors: PINK1 kinase activity requires ATP. PRKN E3 ligase activity requires ATP and ubiquitin. PINK1–Parkin–mitophagy is induced by mitochondrial depolarization. Pharmacologic mitophagy inducers include urolithin A (Mitopure, 500–1000 mg/day; D'Amico 2021 Cell Reports Med), spermidine (1–3 mg/day; Eisenberg 2009 Nat Cell Biol), and rapamycin via mTORC1 inhibition (lifespan extension in mice; ITP NIA studies). Levers: aerobic exercise; fasting/IF; urolithin A; spermidine (wheat germ, aged cheese); rapamycin (off-label longevity dosing).*

## 3.10 mtDNA — replication, maintenance, haplogroup background

The mtDNA itself contributes both Mendelian variants (LHON, MELAS, NARP, Leigh) and haplogroup-level effects through linked combinations of common variants. Nuclear-encoded mtDNA-maintenance proteins (POLG, POLG2, TWNK, RRM2B) cause autosomal mitochondrial DNA depletion or maintenance syndromes when mutated.

| Gene | Variant / rsID | Functional consequence | Source | Risk / directio |
|---|---|---|---|---|

| | | | | n |
|---|---|---|---|---|
| **POLG** | Rare pathogenic missense (e.g. p.W748S, p.A467T, p.Y955C) | mtDNA polymerase γ catalytic subunit; pathogenic variants cause progressive external ophthalmoplegia (PEO), Alpers-Huttenlocher syndrome, ataxia-neuropathy syndromes (SANDO), MNGIE phenocopy. >300 reported variants. Carriers MUST avoid valproate (fatal hepatotoxicity) | *Naviaux 1999 Ann Neurol; OMIM 174763; PharmGKB Level 1A for valproate* | Pathogenic; valproate contraindication |
| **POLG2** | Rare | POLG accessory subunit; rare LoF causes adPEO | *Longley 2006 Am J Hum Genet* | Mendelian |
| **TWNK (Twinkle)** | Rare LoF | Mitochondrial helicase; rare LoF causes adPEO and IOSCA (infantile-onset spinocerebellar ataxia) | *Spelbrink 2001 Nat Genet* | Mendelian |
| **RRM2B** | Rare | Ribonucleotide reductase M2B subunit; mtDNA depletion syndrome | *Bourdon 2007 Nat Genet* | Mendelian |
| **mtDNA haplogroup H** | m.7028C>T-defined; ~40% of Europeans | Reference haplogroup; highest OXPHOS coupling efficiency; lowest baseline ROS | *Gómez-Durán 2010 Hum Mol Genet* | Reference |
| **mtDNA haplogroup J** | m.4216T>C (MT-ND1) + m.13708G>A (MT-ND5) | Mildly reduced Complex I activity; lower ATP, lower ROS; longevity-associated in N. Italian, Irish, Finnish cohorts; not replicated in S. Italian/Spanish; AMPLIFIES LHON penetrance ~3-fold; modest PD-protective signal in some cohorts | *De Benedictis 1999 FASEB J; Ross 2001 Exp Gerontol; Niemi 2005 Hum Hered; Brown 2002 Am J Hum Genet (LHON); Dato 2004 Eur J Hum Genet (no longevity signal in S. Italy)* | J = mixed; longevity in some cohorts; LHON amplifier |
| **mtDNA haplogroup K** | Multiple defining SNPs including m.T9716C | Increased in centenarians (French, Irish, Finnish, US Utah); subhaplogroup K2 with m.T9716C linked to lower all-cause and cardiac mortality | *Raule 2014 Aging Cell; Schulze 2018 bioRxiv; Kenney 2014 PLoS One* | K = longevity association |
| **mtDNA haplogroup U (subgroups)** | Multiple SNPs | U5 = oldest European haplogroup; mild PD-protective signal | *Pyle 2005 Ann Neurol* | U5 mild PD protection |
| **mtDNA m.10398G** | Defines N branch (G) vs M | ND3 missense (Thr114Ala); affects Complex I activity; some PD-risk | *Ghezzi 2005 Eur J Hum Genet;* | Modest PD |

| | | | | |
|---|---|---|---|---|
| **>A** | branch (A) | modulation | *Pyle 2005* | modulation |

*Cofactors: POLG requires dNTPs and $Mg^{2+}$. mtDNA replication depends on adequate nucleotide salvage (TK2, DGUOK, RRM2B). Practical levers: avoid POLG-toxic drugs in carriers (valproate; antivirals d4T, ddI, AZT, fialuridine); maintain B-vitamin status (B1 for thiamine pyrophosphate / TPP; B2 for FAD); ensure iron sufficiency for Fe-S clusters but avoid iron overload. mtDNA copy number is responsive to aerobic exercise (Menshikova 2006 J Gerontol).*

## 4. Summary Table — Categories, Genes, Cofactors, Supplement Targets

This consolidated map links each functional category to its key genes, the cofactors / substrates required for the encoded enzymes, and the supplement, dietary, or behavioral lever that can support each pathway node.

| Functional category | Genes | Cofactors / substrates | Supplement / lifestyle targets |
|---|---|---|---|
| **1. Biogenesis (transcriptional)** | PPARGC1A, PPARGC1B, NRF1, GABPA, TFAM, ESRRA, ERRγ | AMPK (energy stress), SIRT1 + $NAD^+$, ATP, $Mg^{2+}$, zinc | Aerobic exercise, resistance training, cold exposure, fasting/CR, $NAD^+$ precursors, polyphenols (resveratrol, pterostilbene) |
| **2. $NAD^+$ supply** | NAMPT, NMRK1, NMRK2, NMNAT1–3, NADSYN1, NAPRT, CD38 | Tryptophan, niacin (B3), nicotinamide (NAM), nicotinamide riboside (NR), NMN, ATP, PRPP | NR (300–1000 mg/d), NMN (250–500 mg/d), niacin/nicotinamide, CD38 inhibitors (apigenin, quercetin), exercise |
| **3. Sirtuins / FOXO3** | SIRT1, SIRT3, SIRT4, SIRT5, FOXO3 | $NAD^+$ (obligate cosubstrate; consumed stoichiometrically), zinc (SIRT3 zinc finger) | $NAD^+$ precursors; resveratrol/pterostilbene (SIRT1 activators); fasting/IF; ketogenic state; exercise |
| **4. OXPHOS Complexes I–V** | NDUFS, NDUFA, SDHA–D, UQCR, COX, ATP5; mtDNA-encoded ND1–6, CYB, CO1–3, ATP6/8 | FMN (B2), FAD (B2), Fe-S clusters (iron, sulfur), heme (iron, B6), copper (Cu sites), $CoQ_{10}$, cytochrome c | B2 (riboflavin) sufficiency, iron sufficiency (avoid overload), copper, selenium for Fe-S biogenesis, NAC for cysteine, taurine |
| **5. $CoQ_{10}$ biosynth & recycling** | COQ2, COQ3, COQ4, COQ6, COQ7, COQ8A/B, PDSS1/2, NQO1, NQO2 | Tyrosine, mevalonate (HMGCR-dependent), B6 (P5P), B2 (FAD), B3 ($NAD^+$), vitamin C, folate, methionine (SAM), NAD(P)H | Ubiquinol 100–300 mg/d (preferred over ubiquinone in NQO1 P187S T-allele or statin users); fat for absorption; PQQ (synergistic) |

| Functional category | Genes | Cofactors / substrates | Supplement / lifestyle targets |
|---|---|---|---|
| **6. Uncoupling / proton leak** | UCP1, UCP2, UCP3, SLC25A4 (ANT1) | Free fatty acids (activator), 4-HNE (activator), GDP/GTP/ATP/ADP (inhibitors) | Cold exposure (BAT activation), polyunsaturated fats (omega-3), exercise, thermogenic spices (capsaicin) |
| **7. ROS / antioxidant defense** | SOD1, SOD2, SOD3, GPX1, GPX4, CAT, PRDX3, PRDX5, TXN2, TXNRD2, NFE2L2 (NRF2), KEAP1, GSTs, GCLC, GCLM, HMOX1 | $Mn^{2+}$ (SOD2), Cu/Zn (SOD1/3), selenocysteine (GPX, TXNRD), heme/Fe (CAT), GSH (cysteine + glycine + glutamate), thioredoxin | Sulforaphane/ glucoraphanin (NRF2 activator), NAC/NACET (cysteine donor), glycine, selenium 100–200 µg, manganese, alpha-lipoic acid, curcumin |
| **8. Dynamics: fusion / fission** | MFN1, MFN2, OPA1, DNM1L (DRP1), MFF, FIS1, MID49, MID51 | GTP (all GTPases), CDK1/PKA (DRP1 phospho-regulation) | Exercise (raises MFN2); cold (drives fission); AMPK activation (metformin) modulates |
| **9. Mitophagy / quality control** | PINK1, PRKN, PARK7, OPTN, NDP52, BNIP3, BNIP3L (NIX), FUNDC1 | ATP (kinase + ligase activity), ubiquitin, LC3 | Urolithin A (Mitopure 500–1000 mg/d), spermidine (wheat germ, aged cheese), rapamycin (off-label), aerobic exercise, fasting/IF |
| **10. mtDNA maintenance** | POLG, POLG2, TWNK, SSBP1, RRM2B, TFAM (also in cat 1); mtDNA haplogroups | dNTPs, $Mg^{2+}$, B-vitamins for nucleotide synthesis | Avoid POLG-toxic drugs (valproate, d4T, ddI, AZT) in carriers; maintain B1, B2; iron sufficiency without overload; aerobic exercise raises copy number |

## 5. Complete SNP rsID Lookup Table

Reference table of all rsIDs catalogued in this document with GRCh38 coordinates, REF/ALT alleles (forward strand convention as reported by dbSNP), and concise interpretation. The 'risk' allele is the one associated with reduced enzyme function or increased disease risk; for some longevity loci, the 'beneficial' allele is noted instead. For minus-strand-encoded genes (notably SOD2, NQO1, MTHFR-style cases), the dbSNP forward-strand REF/ALT may appear as the reverse complement of the canonical literature notation; the 'Notes' column flags these cases.

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| **rs8192678** | PPARGC1A | Gly482Ser, c.1444G>A | chr4:23814039 | C>T | Coding missense; T (Ser482) reduces PGC-1α activity; risk for T2D, NAFLD; endurance |

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| | | | | | underperformance |
| **rs7665116** | PPARGC1A | Intronic | chr4:23900431 | G>A | HD age-of-onset modifier |
| **rs3856806** | PPARGC1A | Thr528Thr (syn) | chr4:23814104 | C>T | Tag SNP; modest T2D/obesity |
| **rs2970847** | PPARGC1A | Thr394Thr (syn) | chr4 (PPARGC1A locus) | G>A | Tag SNP; modest |
| **rs6949152** | NRF1 | Intronic | chr7:129642511 | A>G | A/A → higher MHC-I (slow-twitch) in women; HD modifier |
| **rs7781972** | NRF1 | Tag | chr7 (NRF1 locus) | C>T | HD age-of-onset modifier |
| **rs1882094** | NRF1 | Non-syn | chr7 (NRF1 locus) | C>T | Modifier |
| **rs3735006** | NRF1 | Non-syn | chr7 (NRF1 locus) | C>T | Modifier |
| **rs1937** | TFAM | Ser12Thr, coding | chr10:58385450 | G>C | C (Thr) longevity-associated in Chinese CLHLS (n=3,294) |
| **rs2306604** | TFAM | Intronic | chr10:58385601 | A>G | TFAM expression / mtDNA copy number |
| **rs3217060** | ESRRA | 23-bp microsatellite (promoter) | chr11:64148631 | VNTR | HD age-of-onset modifier |
| **rs3753579** | MFN2 | Promoter | chr1:11910671 | C>T | HD age-of-onset modifier |
| **rs1319501** | NAMPT | -948G>T (promoter) | chr7:106248081 | G>T | T → reduced NAMPT transcription; lower eNAMPT/visfatin |
| **rs2058539** | NAMPT | Intronic | chr7 (NAMPT locus) | C>T | T2D / metabolic-syndrome tag SNP |
| **rs10487819** | NAMPT | Intronic | chr7 (NAMPT locus) | C>T | Tag SNP |
| **rs12785878** | NADSYN1 | Intronic | chr11:71434591 | G>T | Vit-D 25-OH level locus; D-NAD axis |
| **rs1130169** | CD38 | Intronic | chr4:15518231 | C>T | CD38 expression; $NAD^+$-consumer |

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| **rs11555236** | SIRT3 | Intronic | chr11:215627 | A>G | Treviso Longeva longevity association |
| **rs3782116** | SIRT3 | VNTR-adjacent enhancer | chr11:215101 | varies | Long-allele Italian centenarians; not replicated in French |
| **rs939915** | SIRT3 | Tag | chr11:215651 | C>T | Positive in meta-analysis |
| **rs3825075** | SIRT3 | Tag | chr11:215101 | C>T | Tested in centenarians |
| **rs4980329** | SIRT3 | Tag | chr11:215651 | C>T | Tested in centenarians |
| **rs511744** | SIRT3 | Tag | chr11:215801 | C>T | Tested in centenarians |
| **rs7934919** | SIRT3 | Tag | chr11 (SIRT3 locus) | C>T | Tested in centenarians |
| **rs1045288** | SIRT3 | 3'-UTR | chr11 (SIRT3 locus) | C>T | Tested in centenarians |
| **rs559422** | SIRT3 | Tag | chr11 (SIRT3 locus) | C>T | Tested in centenarians |
| **rs3817630** | SIRT3 | Tag | chr11 (SIRT3 locus) | C>T | Tested in centenarians |
| **rs2293168** | SIRT3 | Tag | chr11 (SIRT3 locus) | G>A | Tested in centenarians |
| **rs2802292** | FOXO3 | Intronic enhancer (HSF1 site) | chr6:108587315 | T>G | G = longevity allele; HSF1-induced FOXO3 expression; +1.9-fold odds 95+ in HALE |
| **rs13217795** | FOXO3 | Intronic | chr6:108560721 | T>C | Longevity LD block |
| **rs2253310** | FOXO3 | Intronic | chr6:108587001 | C>G | Longevity LD block |
| **rs2764264** | FOXO3 | Intronic | chr6:108587101 | T>C | Longevity LD block |
| **rs9400239** | FOXO3 | Intronic | chr6:108600001 | C>T | Longevity-associated |
| **rs4946935** | FOXO3 | Intronic | chr6:108560001 | G>A | SRF binding-site disruption (A allele) |

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| **rs4880** | SOD2 | V16A, c.47T>C (gene strand); minus-strand gene | chr6:159692840 | A>G (forward) | T (Val16) on gene strand = A on dbSNP forward = RISK for low MnSOD activity, T1D nephropathy, OSA severity, depression. C (Ala16) on gene strand = G on forward = beneficial |
| **rs2855116** | SOD2 | Intronic | chr6 (SOD2 locus) | G>A | LD with rs4880 |
| **rs5746136** | SOD2 | 3'-region | chr6 (SOD2 locus) | C>T | LD with rs4880; BC association |
| **rs1050450** | GPX1 | Pro198Leu, c.593C>T | chr3:49357401 | C>T | T (Leu) = reduced enzyme; selenium-rescuable; CHD risk |
| **rs1001179** | CAT | -262C>T (promoter) | chr11:34438681 | C>T | T = lower erythrocyte catalase activity; CVD risk |
| **rs769214** | CAT | Promoter | chr11:34438701 | G>A | Promoter tag SNP |
| **rs769217** | CAT | 5'-UTR | chr11:34438721 | C>T | Tag SNP |
| **rs6721961** | NFE2L2 (NRF2) | -617C>A (promoter ARE) | chr2:177230305 | C>A | A = RISK; reduced NRF2 self-induction; T2D OR 1.56 (AA vs CC); endothelial vasodilator impairment |
| **rs35652124** | NFE2L2 | -274A>G (promoter) | chr2:177229898 | T>C | G/C reduces ARE binding; CV mortality in HD; ALD susceptibility |
| **rs2886162** | NFE2L2 | Tag | chr2 (NFE2L2 locus) | G>A | Lung-function modifier |
| **rs1806649** | NFE2L2 | Tag | chr2 (NFE2L2 locus) | C>T | Tag SNP |
| **rs7557529** | NFE2L2 | Tag | chr2 (NFE2L2 locus) | C>T | Tag SNP |
| **rs2706110** | NFE2L2 | Tag | chr2 (NFE2L2 locus) | C>T | Tag SNP |
| **rs5748469** | TXNRD2 | Intronic | chr22 (TXNRD2 locus) | C>T | Mito thioredoxin reductase; modest CV signals |
| **rs1695** | GSTP1 | Ile105Val, c.313A>G | chr11:67585219 | A>G | G (Val) = reduced enzymatic activity for electrophiles; mixed cancer risk |

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| **rs4986894** | GSTM1 | Promoter region tag | chr1 (GSTM1 locus) | varies | Tag SNP — actual GSTM1-null status requires CNV assay (whole-gene deletion) |
| **rs1800566** | NQO1 | Pro187Ser, c.559C>T (gene strand); minus-strand gene | chr16:69711242 | G>A (forward) | A on dbSNP forward = T on gene strand = Ser187 = LoF (T/T has no NQO1 protein/activity); risk for CoQ recycling impairment, drug toxicity, breast/lung/colon cancer |
| **rs1143684** | NQO2 | Leu47Phe, c.139C>T | chr6:74060219 | C>T | T (Phe) modestly reduces NQO2; weaker than NQO1 P187S |
| **rs6925344** | COQ3 | Gly272Ser, c.814G>A | chr6:98091201 | G>A | Modest CoQ-status effects |
| **rs8500** | COQ6 | Met406Val, c.1216A>G | chr14:74404951 | A>G | Modest |
| **rs11074359** | COQ7 | Met103Thr | chr16:19075901 | T>C | Modest |
| **rs6818847** | COQ2 | Intronic | chr4:83559951 | C>T | MSA risk and statin myopathy susceptibility |
| **rs659366** | UCP2 | -866G>A (promoter) | chr11:73959540 | G>A | A = increased premature CAD risk (recessive); G = longevity haplotype; context-dependent |
| **rs660339** | UCP2 | Ala55Val, c.164C>T | chr11:73959241 | C>T | T/T = higher visceral fat, MetS risk |
| **rs1800849** | UCP3 | -55C>T (promoter) | chr11:73987961 | C>T | T allele mixed; favorable longevity in Italian; high VAF |
| **rs1800592** | UCP1 | -3826A>G (promoter) | chr4:140560269 | A>G | G reduces UCP1 in BAT; modest BMI |
| **rs6555055** | SDHA | Intronic | chr5 (SDHA locus) | C>T | Modest body-composition signal |
| **rs11538212** | CYCS | Intronic | chr7 (CYCS locus) | C>T | Modest cytochrome c |
| **rs2227956** | HSPA1L | Coding | chr6 (HSP70 locus) | C>T | Mitochondrial HSP70-family chaperone |
| **rs9024** | TFAM | Tag | chr10 (TFAM locus) | C>T | Tag SNP |

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| **rs2228145** | IL6R | Asp358Ala | chr1:154453788 | C>A | Listed for inflammation–mitochondria crosstalk reference |
| **rs6121** | TREH (trehalase) | Coding | chr11 (TREH locus) | C>T | Trehalose pathway; mitochondrial protectant nutrient |
| **rs2287161** | BTBD11 | Tag | chr12 (BTBD11 locus) | C>G | Tag SNP for completeness |

*Region-scan loci (queried as full intervals rather than discrete SNPs): PPARGC1A (chr4:23,793,000–23,892,000), NRF1 (chr7:129,638,000–129,743,000), TFAM (chr10:58,385,000–58,400,000), SIRT3 (chr11:214,000–220,000), FOXO3 (chr6:108,557,000–108,685,000), NFE2L2 (chr2:177,229,000–177,235,000), SOD2 (chr6:159,669,000–159,762,000), NQO1 (chr16:69,708,000–69,723,000), UCP2-UCP3 locus (chr11:73,957,000–73,992,000), POLG (chr15:75,019,000–75,100,000), POLG2 (chr16:66,486,000–66,506,000), TWNK (chr10:100,985,000–101,005,000), MFN2 (chr1:11,910,000–12,030,000), OPA1 (chr3:193,593,000–193,641,000), DNM1L/DRP1 (chr12:32,679,800–32,745,700), PINK1 (chr1:20,633,598–20,651,709), PRKN (chr6:161,347,417–162,727,802), PARK7 (chr1:7,954,290–8,043,800), BNIP3 (chr10:102,295,000–102,327,000), NAMPT (chr7:106,245,000–106,283,000), CD38 (chr4:15,518,000–15,584,000).*

## 6. ClinVar Pathogenicity and PharmGKB Clinical Annotation

ClinVar interpretations and PharmGKB clinical annotation levels for the variants in this reference where evidence is sufficient for assertion. PharmGKB levels: 1A (highest — reviewed CPIC/DPWG guideline); 1B (consistent functional evidence); 2A (moderate, with replication); 2B (functional but limited); 3 (preliminary); 4 (preliminary, single study).

| Gene / variant | ClinVar status | PharmGKB level | Notes |
|---|---|---|---|
| **NQO1 P187S (rs1800566, c.559C>T)** | Drug response (multiple submissions) | PharmGKB Clinical Annotation Level 2B / 3 — anthracycline response, post-chemotherapy leukemia susceptibility | T/T genotype lacks NQO1 protein/activity. Affects ubiquinone recycling, NRF2 stability, p53 stabilization, and metabolism of mitomycin C, anthracyclines (epirubicin), benzene metabolites. Carrier prevalence: ~9,942 T/T homozygotes per 279,866 alleles in gnomAD |
| **POLG rare pathogenic variants (e.g. p.W748S, A467T, Y955C)** | Pathogenic / Likely pathogenic (multiple) | PharmGKB Level 1A — valproate hepatotoxicity contraindication | Mendelian; carriers must avoid valproic acid (FDA boxed warning); avoid d4T, ddI, AZT, fialuridine |
| **MFN2 missense** | Pathogenic / Likely | Not | Charcot-Marie-Tooth 2A; |

| Gene / variant | ClinVar status | PharmGKB level | Notes |
|---|---|---|---|
| **(e.g. R94Q)** | pathogenic | pharmacogenomic | autosomal dominant |
| **OPA1 LoF / dominant-negative** | Pathogenic | Not pharmacogenomic | Autosomal dominant optic atrophy; ~1:30,000 prevalence |
| **DNM1L (DRP1) dominant-negative (e.g. A395D)** | Pathogenic | Not pharmacogenomic | Encephalopathy with refractory epilepsy |
| **PINK1 biallelic LoF** | Pathogenic | Not pharmacogenomic | Autosomal recessive early-onset PD; heterozygotes may have subclinical mitochondrial dysfunction |
| **PRKN biallelic LoF / exon deletions** | Pathogenic | Not pharmacogenomic | Autosomal recessive juvenile PD; heterozygous carriers ~1–2% population prevalence |
| **PARK7 biallelic LoF** | Pathogenic | Not pharmacogenomic | Autosomal recessive PD |
| **mtDNA m.3243A>G (MT-TL1)** | Pathogenic | Not pharmacogenomic (heteroplasmy-dependent) | MELAS at high heteroplasmy; MIDD at lower; maternally inherited |
| **mtDNA m.11778G>A (MT-ND4, LHON)** | Pathogenic | Not pharmacogenomic | Leber's hereditary optic neuropathy; haplogroup-J amplifies penetrance |
| **mtDNA m.3460G>A (MT-ND1, LHON)** | Pathogenic | Not pharmacogenomic | LHON; less common than m.11778 |
| **mtDNA m.14484T>C (MT-ND6, LHON)** | Pathogenic | Not pharmacogenomic | LHON; better recovery prognosis than m.11778; haplogroup-J amplifies |
| **mtDNA m.8993T>G/C (MT-ATP6)** | Pathogenic | Not pharmacogenomic | NARP/Leigh syndrome (heteroplasmy-dependent) |
| **SOD2 V16A (rs4880)** | Risk-factor / drug-response (variable submissions) | Not in current CPIC | Functional polymorphism; T (Val) reduces mitochondrial import; modulates response to platinum chemotherapy, anthracyclines, bleomycin |
| **FOXO3 rs2802292** | Risk-factor (longevity) | Not pharmacogenomic | G allele creates HSF1-binding site; replicated longevity association across populations |
| **NFE2L2 rs6721961** | Risk-factor | Not pharmacogenomic | Promoter ARE motif; affects T2D, lung function, vasodilator response |

*Common-variant entries with no formal ClinVar 'Pathogenic' classification appear in the literature as functional polymorphisms with risk-factor status. PharmGKB clinical annotation levels apply specifically to drug–gene interactions; pharmacogenomic-relevant variants in this pathway are concentrated in NQO1 (anthracycline / mitomycin response) and POLG (valproate hepatotoxicity). Other variants may have pharmacogenomic implications inferable from mechanism (e.g. SOD2 V16A and platinum chemotherapy oxidative stress; CoQ10 supplementation form for NQO1 P187S T-allele carriers and statin users) but lack formal CPIC/DPWG guideline status.*

## 7. Mitochondrial DNA Haplogroup Reference

Mitochondrial haplogroups represent linked combinations of mtDNA SNPs that arose during human migration history. They modulate ETC efficiency, ROS production, susceptibility to LHON penetrance, and aging-related disease risk. In whole-genome sequencing, haplogroup is inferred from the chrM (mtDNA) variants in the VCF. Below, the major European haplogroups are summarized; African and Asian haplogroups are referenced briefly for completeness.

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| **m.7028C >T** | MT-CO1 | Haplogroup-defining (H is reference) | chrM:7028 | C>T | H-haplogroup defining variant |
| **m.4216T >C** | MT-ND1 | Haplogroup J defining | chrM:4216 | T>C | Haplogroup J: mildly reduced Complex I; longevity in some N. European cohorts; LHON penetrance amplifier |
| **m.13708 G>A** | MT-ND5 | Haplogroup J defining | chrM:13708 | G>A | Haplogroup J co-defining |
| **m.10398 G>A** | MT-ND3 | Thr114Ala | chrM:10398 | G>A | Common in non-H haplogroups; modest PD-risk modulation |
| **m.9716T >C** | MT-CO3 | Haplogroup K2 defining | chrM:9716 | T>C | Haplogroup K2: reduced all-cause and cardiac mortality (Raule 2014) |
| **m.11778 G>A** | MT-ND4 | LHON primary mutation | chrM:11778 | G>A | Most common LHON; ~50% male / 10% female penetrance; haplogroup J amplifies |
| **m.3460G >A** | MT-ND1 | LHON primary mutation | chrM:3460 | G>A | Less common LHON; haplogroup J amplifies |
| **m.14484 T>C** | MT-ND6 | LHON primary mutation | chrM:14484 | T>C | Most recoverable LHON; haplogroup J amplifies |

| rsID | Gene | Variant | GRCh38 position | REF/ ALT | Notes |
|---|---|---|---|---|---|
| **m.3243A >G** | MT-TL1 | MELAS / MIDD | chrM:3243 | A>G | tRNA-Leu(UUR); MELAS at high heteroplasmy |
| **m.8993T >G or T>C** | MT-ATP6 | NARP / Leigh | chrM:8993 | T>G or T>C | Heteroplasmy-dependent NARP/Leigh |

*European haplogroup frequencies (approximate): H 40–50%, U 15–20% (U5 ~10% in N. Europe), K 8–11%, J 8–10%, T 7–9%, V 5–7%, W/X/I 1–3% each. African haplogroups (L0, L1, L2, L3) define the ancestral root. Asian haplogroups (M, N derived branches; A, B, C, D, F sub-branches). Haplogroup determination from a WGS VCF can be done with HaploGrep2 or HmtDB; full mtDNA tree is at PhyloTree.org.*

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*This document is a generic educational reference and does not contain personal genotype data, medication or supplement regimens, or individualized clinical recommendations. It is intended to be paired with a separate personalized analysis if applied to a specific individual's whole-genome sequencing or genotyping data. Variant interpretations should be revisited as new GWAS, mechanistic, or pharmacogenomic evidence accumulates.*