Proteostasis / Autophagy / Unfolded Protein Response

Genetic Pathway Reference

Chaperones, ER stress sensors, ubiquitin-proteasome handoff, autophagy, and lysosomal clearance

9 functional categories • ~46 SNPs catalogued • ~36 gene-region scans

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of cellular proteostasis — the integrated network of protein synthesis, folding, trafficking, surveillance, and degradation that maintains a functional proteome. It catalogues the genes that govern cytosolic chaperones (HSP70 family, HSF1, small HSPs, DNAJ co-chaperones), the endoplasmic reticulum unfolded protein response (UPR; PERK, IRE1, ATF6, BiP), the core autophagy machinery (ATG conjugation systems, BECN1, LC3 family), selective autophagy receptors (SQSTM1/p62, OPTN), mitophagy adapters (PINK1, Parkin, DJ-1), the lysosomal compartment (TFEB, LAMP2, GBA1, VPS35 retromer), and the master upstream regulators that integrate nutrient and stress signals into proteostasis output (FOXO3, SIRT1, mTOR). For each gene, well-studied common and rare variants are catalogued with their functional consequence, cofactor or substrate dependencies (where applicable), ClinVar pathogenicity status when relevant, and the supplement, dietary, behavioral, or pharmacologic targets that map to each pathway node.

All variant interpretations are based on published GWAS literature, peer-reviewed mechanistic studies, ClinVar records, and replicated meta-analyses through 2026. Sources include Science, Nature, Nature Genetics, Nature Communications, Cell, EMBO Journal, EMBO Reports, PNAS, Acta Neuropathologica, Brain, Human Molecular Genetics, Journal of Bone and Mineral Research, Hepatology, Journal of Neurology, Autophagy, Cell Stress and Chaperones, Annual Review of Biochemistry, OMIM, ClinVar, and the GWAS Catalog. The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations.

Proteostasis is a broad, polygenic, and highly pleiotropic phenotype: virtually every late-onset neurodegenerative and protein-aggregation disease has proteostasis failure at its core. Most common variants catalogued here confer modest individual effects (odds ratios of 1.1–2.0 for the relevant phenotype). A small number of rare large-effect variants in HSPB1 (CMT2F/dHMN), SQSTM1 (Paget disease, ALS, FTD, distal myopathy), LAMP2 (Danon disease, X-linked), GBA1 (Gaucher disease and Parkinson's risk), VPS35 (familial PD), PINK1 / PRKN (recessive juvenile PD), and EIF2AK3 (Wolcott-Rallison syndrome when biallelic) are catalogued for completeness even though their population frequency is below 1%.

Heritability anchors: most autophagy / UPR phenotypes are not classical heritable traits; instead, their genetic effects are seen on (i) age-related disease risk (PSP, Crohn's, Paget, ALS-FTD, NAFLD progression, atherosclerosis), (ii) longevity itself (FOXO3 rs2802292 increases probability of reaching 95+ by ~1.9-fold; Willcox PNAS 2008; Bao npj Aging 2024), and (iii) tissue-specific stress vulnerability (e.g., bone mineral density and PSP risk for EIF2AK3 haplotype B; Liu JBMR 2012; Höglinger Nat Genet 2011).

2. Pathway Biology

2.1 The proteostasis network — three pillars and one integrator

Proteostasis is the integrated cellular system that keeps the proteome functional: it synthesizes proteins, folds them, traffics them, surveys them for damage, and clears them when they become misfolded, damaged, or redundant. The network has three classical pillars — chaperone-assisted folding, the ubiquitin-proteasome system (UPS) for soluble protein turnover, and autophagy for bulk cargo and aggregate clearance — and one master transcriptional integrator, TFEB, that coordinates lysosomal biogenesis with autophagy in response to mTORC1 status (Settembre et al., Science 2011; Sardiello et al., Science 2009; Takla et al., EMBO Reports 2023). Across all metazoan models studied — yeast, C. elegans, Drosophila, mouse, primate — proteostasis capacity declines with age, and interventions that augment any pillar (rapamycin, dietary restriction, polyamines, exercise) extend lifespan or healthspan.

2.2 Chaperone-assisted folding and the heat shock response

HSP70 family proteins (HSPA1A, HSPA1B inducible; HSPA1L constitutive; HSPA8 cognate; HSPA5/BiP in the ER) are ATP-dependent chaperones that bind nascent and partially-folded clients via a substrate-binding domain and either fold them, refold misfolded forms, or hand them off for degradation. They work with HSP90 and small HSPs (HSPB1/HSP27, HSPB8, αB-crystallin) and require DNAJ/HSP40 co-chaperones to recruit specific clients. The transcription factor HSF1 senses unfolded protein load — sequestered by HSP70/HSP90 in the basal state, released when client demand rises — and drives expression of the entire chaperone arm. HSF1 activity declines with normal aging and is preserved or enhanced in long-lived rodent models (Singh & Aballay, Cell Stress Chaperones 2024; Calderwood et al., 2009).

2.3 The endoplasmic reticulum UPR

Roughly one-third of the proteome is folded in the ER, where load-sensing is performed by three transmembrane sensors held inactive by the ER chaperone BiP (HSPA5). When unfolded protein accumulates, BiP releases the sensors. PERK (encoded by EIF2AK3) phosphorylates eIF2α, halting global cap-dependent translation while paradoxically permitting ATF4 translation; IRE1α (encoded by ERN1) splices XBP1 mRNA into the active XBP1s transcription factor; ATF6 translocates to the Golgi and is cleaved, releasing a cytoplasmic transcription factor fragment. Together they expand ER folding capacity, induce ER-associated degradation (ERAD), and, if stress is unresolved, trigger CHOP (DDIT3)-driven apoptosis (Hetz et al., Nat Rev Mol Cell Biol 2020; Walter & Ron, Science 2011; Hughes et al., Brain 2016).

2.4 Ubiquitin-proteasome system and selective tagging

Soluble proteins flagged for destruction are tagged with K48-linked polyubiquitin chains by E1-E2-E3 cascades and delivered to the 26S proteasome. Mitophagy uses K6/K11/K63 chains assembled by Parkin (PRKN), an E3 ligase activated by PINK1 phosphorylation on damaged mitochondria. PARK7/DJ-1 contributes redox sensing. Selective autophagy receptors — most notably p62 (SQSTM1) — bridge ubiquitinated cargo to the LC3-decorated autophagosome via a UBA domain (cargo) and an LIR motif (LC3 binding). p62 also binds KEAP1 via a KIR motif, integrating proteostasis with the Nrf2 oxidative stress response (Komatsu, Pickrell & Youle, Nat Cell Biol 2018; Lazarou et al., Nature 2015).

2.5 Autophagy machinery

Macroautophagy proceeds in defined steps: (i) initiation by the ULK1 complex when AMPK is active or mTORC1 is inhibited; (ii) nucleation of the phagophore by Beclin-1 (BECN1) / Class III PI3K (VPS34); (iii) elongation requiring two ubiquitin-like conjugation systems — ATG12-ATG5-ATG16L1 (E1: ATG7; E2: ATG10) and LC3-PE (E1: ATG7; E2: ATG3); (iv) cargo recognition by p62 / NBR1 / OPTN / NDP52 / TAX1BP1; (v) lysosomal fusion via LAMP2, syntaxin-17, and the HOPS complex; (vi) cargo degradation by lysosomal hydrolases including GBA1 (glucocerebrosidase), CTSD (cathepsin D), and others; (vii) lysosomal reformation. Chaperone-mediated autophagy (CMA) is a parallel pathway in which LAMP2A is the receptor for KFERQ-motif-containing cytosolic proteins, with HSC70 (HSPA8) as the cargo carrier (Klionsky et al., Autophagy 2021; Cuervo & Wong, Cell Res 2014).

2.6 The TFEB-mTOR axis and master regulators

TFEB is the master transcription factor for lysosomal biogenesis and autophagy, binding the CLEAR consensus motif in target gene promoters. mTORC1 at the lysosomal surface phosphorylates TFEB on Ser211 (and Ser142, Ser122), keeping it cytosolic via 14-3-3 binding. Starvation, lysosomal stress, exercise, and pharmacological mTOR inhibition (rapamycin) dephosphorylate TFEB, allowing nuclear translocation and induction of ~500 lysosomal/autophagy genes (Settembre Science 2011; Takla EMBO Rep 2023). FOXO3, downstream of insulin/IGF-1/Akt signaling, is a parallel transcriptional driver of autophagy genes (LC3B, BNIP3, GABARAPL1) and stress-resistance genes (SOD2, CAT, GADD45A); the rs2802292 G allele in FOXO3 creates an HSF1 binding site in an intronic enhancer, directly coupling the heat-shock response to FOXO3-driven autophagy (Donlon et al., NAR 2018; Bao npj Aging 2024). SIRT1 deacetylates HSF1 (extending its DNA-binding) and FOXO3, linking NAD+ availability to proteostasis output.

2.7 Cross-talk with other pathways and disease links

Proteostasis intersects with virtually every aging-relevant pathway. mTOR couples nutrient sensing to autophagy suppression (rapamycin/mTOR report). FOXO3 couples insulin/IGF-1 signaling to autophagy (IGF1 report). Mitophagy via PINK1/Parkin couples ATP and ROS production to organelle clearance (Mitochondrial report). GBA1, VPS35, LRRK2, and α-synuclein converge on lysosomal handling of α-synuclein in Parkinson's disease (PD report). HSF1-FOXO3 coupling provides a longevity-relevant heat-shock-to-stress-response axis. ATG16L1 T300A increases ER stress and inflammation in IBD and lung-transplant rejection (Inflammation/Immune report). EIF2AK3 haplotype B reduces bone mineral density (Bone report) and increases PSP risk (Dementia report). Many proteostasis genes are also pharmacogenes (rapamycin/sirolimus targets mTOR; HCQ/CQ target lysosomal pH; bortezomib targets the proteasome) — see the Pharmacogenomics report for actionable PGx variants.

3. Functional Categories: Genes, Variants, and Cofactors

3.1 Cytosolic HSP70 family and HSF1 (chaperone-assisted folding)

The HSP70 family in humans includes the heat-inducible HSPA1A and HSPA1B (encoding identical mature proteins from a tandem duplication in the HLA class III region on chromosome 6p21.3), the constitutively-expressed HSPA1L (testis-enriched but broadly expressed), the cognate HSPA8 (HSC70, also a CMA cargo carrier), and the ER-resident HSPA5 (BiP). All require ATP and Mg^{2+} for the substrate-binding/release cycle and rely on DNAJ co-chaperones

to deliver clients. HSF1 is the master transcription factor for the heat-shock response and is a documented longevity factor in invertebrate models.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
HSPA1A	rs1043618 (5'UTR +190 G>C)	5'UTR variant; C allele reduces HSP70 translation efficiency (~14–45% lower luciferase reporter); CC homozygotes show lower intragranulocytic HSP70	He 2009 PLoS ONE; Jin 2012	C → ↑ CHD risk OR 1.56; ↑ atherosclerosis
HSPA1A	rs1008438 (-110 A>C, promoter)	Promoter polymorphism; CC reduces HSP70 production	He 2009; Jin 2012; Marin 2012	C → ↑ COPD risk in smokers OR 1.52
HSPA1L	rs2227956 (T493M, exon 9)	Nonsynonymous Thr→Met in substrate-binding domain; subtle structural change	Spagnolo 2007; Vargas-Alarcon 2015; Lin 2024	G/Met allele → ↓ IPF risk OR 0.24; ↑ NIHL risk in Caucasians
HSPA1L	rs2075800 (E272K)	Nonsynonymous Glu→Lys in NBD-SBD linker; alters substrate handling	Spagnolo 2007; Vargas-Alarcon 2015	T/T → ↑ IPF susceptibility OR 2.52
HSPA1B	rs1061581 (Q351Q, +1267 G>A)	Synonymous; in LD with regulatory variants	Vargas-Alarcon 2015; Zong 2020; Bogunia-Kubik 2007	A → ↓ IPF OR 0.27 (recessive); ↑ preeclampsia OR 1.87 in Han Chinese; mixed schizophrenia / vitiligo data
HSPA1B	rs2763979 (5' regulatory)	5' flanking; modulates basal expression	Konings 2007; Chang 2017; Hsu 2021	T → ↓ age-related hearing loss; ↑ NIHL TT genotype

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
HSPA8 (HSC70)	rs1136141, rs2236659	Cognate HSP70; CMA cargo carrier; rare functional studies	Wisniewska 2010	Speculative
HSPA5 (BiP)	rs391957 (-415 G>A)	ER chaperone master regulator of UPR; promoter variant	Zhu 2007; Wang 2022 lung cancer	Risk allele → ↑ lung cancer risk in Chinese
HSF1	common variants poorly characterized	Master HSR transcription factor; sustained activity associated with longevity in C. elegans, Ames dwarf mice; gene-region scan recommended	Akerfelt et al., Nat Rev Mol Cell Biol 2010; Singh Cell Stress Chap 2024	Mostly model-organism evidence

Cofactors: ATP and Mg^{2+} for the HSP70 ATPase cycle. Aging reduces HSF1 DNA-binding activity. Practical levers: heat-stress (sauna, hot baths) induces HSP70 (Brunt et al., J Physiol 2016, 2018); endurance exercise, aerobic training, and short-term fasting all activate HSF1; SIRT1 activators (NAD+ precursors) deacetylate and prolong HSF1 binding (Westerheide Science 2009).

3.2 Small heat shock proteins (HSPB1, CRYAB)

Small HSPs are ATP-independent holdases with a conserved α-crystallin domain. They bind aggregation-prone clients in folding-competent states and prevent irreversible aggregation under stress. Both HSPB1 (HSP27) and HSPB8 are HSF1-induced. Mutations in the α-crystallin domain cause autosomal-dominant motor and sensorimotor neuropathies.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
HSPB1 (HSP27)	S135F, R136L/W, P182L (rare missense)	α-crystallin domain disruption; oligomerization defect; reduced chaperone activity toward neurofilaments and microtubules	Evgrafov 2004 Nat Genet; Almeida-Souza 2010 J Biol Chem	Autosomal dominant; CMT2F / dHMN2; very rare
HSPB1	common SNPs (rs2868370, rs2868371)	Promoter variants; modest effects on cardiovascular phenotypes; not strongly replicated	—	Speculative; gene-region scan recommended
CRYAB (αB-crystallin)	R120G (rare)	α-crystallin domain disruption; myofibrillar myopathy with cataracts	Vicart 1998 Nat Genet	Autosomal dominant; rare
HSPB8	K141E, K141N	α-crystallin domain; CMT2L /	Irobi 2004 Nat	Autosom

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
	(rare)	dHMN2A	Genet	al dominant ; very rare

Cofactors: small HSPs are ATP-independent; phosphorylation by p38 MAPK / MK2 regulates their oligomerization state. Practical levers: heat-stress and endurance exercise induce HSPB1; estrogen modulates HSPB1 expression.

3.3 DNAJ / HSP40 co-chaperones (substrate delivery)

DNAJ proteins contain a conserved J-domain that stimulates HSP70 ATPase activity and delivers specific clients. Three subfamilies (A/B/C) with ~50 members in humans cover diverse client repertoires. Most clinically relevant variants are rare loss-of-function mutations causing autosomal-recessive disease; common-variant proteostasis associations are sparse.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
DNAJB6	rare F89I, F93L, P96R	α-synuclein and polyglutamine aggregation suppressor; LGMDD1 mutations	Sarparanta 2012 Nat Genet; Aprile-Garcia 2019 Nat Cell Biol	Autosom al dominant LGMDD1 ; very rare
DNAJB1	common SNPs	Cytosolic HSP40; not strongly disease-associated	—	Speculati ve
DNAJC6 (auxilin-1)	Q734X, R927G (rare)	Loss of function; juvenile-onset autosomal recessive PD (PARK19)	Olgiati 2016 Ann Neurol; Edvardson 2012 PLoS ONE	Autosom al recessive ; cross-ref PD report
DNAJC13 (RME-8)	N855S (rs387907571) — debated	Originally linked to dominant late-onset PD in Mennonite family; NOT replicated in 2025 AMP-PD analysis	Vilarino-Güell 2014 Hum Mol Genet; AMP-PD 2025 medRxiv	Evidence currently weak
DNAJC12	rare biallelic LoF	BH4-responsive hyperphenylalaninemia and parkinsonism	Anikster 2017 Am J Hum Genet	Autosom al recessive ; very rare
DNAJC10 (ERdj5)	common SNPs	ER-resident; ERAD reductase; PD-modifier candidate	Lithgow lab	Speculati ve

Cofactors: J-domain co-chaperones use ATP indirectly via HSP70 cycle. Most disease-causing DNAJ variants are private and require gene-panel sequencing rather than rsID-based queries; accordingly we use gene-region scans for these in the Phase 3 query.

3.4 ER unfolded protein response (PERK, IRE1, ATF6, BiP, downstream)

The UPR is the ER's load-management system. Of the three sensors, PERK (EIF2AK3) has the most robust common-variant association in human disease — the PERK-B haplotype, defined by three nonsynonymous SNPs (rs867529, rs13045, rs1805165) in linkage with the intronic GWAS-significant rs7571971, is associated with progressive supranuclear palsy (PSP) and lower bone mineral density. Rare biallelic LoF mutations in EIF2AK3 cause Wolcott-Rallison syndrome.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
EIF2AK3 (PERK)	rs7571971 (intron 2)	GWAS-significant tag SNP for PERK haplotype B; perfect LD with coding SNPs	Höglinger 2011 Nat Genet (PSP GWAS, p = 3.2×10^{-13})	Risk haplotype B; ~28% global carrier frequency
EIF2AK3	rs13045 (Q166R or R166Q)	Nonsynonymous; haplotype B coding tag	Liu 2012 JBMR; Yuan 2018 Hum Mol Genet	Minor allele → ↓ BMD, ↑ PSP, ↑ ER-stress sensitivity in vitro
EIF2AK3	rs867529 (S136C)	Nonsynonymous; haplotype B coding tag	Liu 2012 JBMR; Stutzbach 2013 Acta Neuropathol Commun; Ma 2024 Sci Rep (PERK-B knock-in)	Minor allele → ↑ PSP risk; ↑ growth hormone deficiency; HIV neurocognitive impairment
EIF2AK3	rs1805165 (S704A or A704S)	Nonsynonymous; haplotype B coding tag	Liu 2012 JBMR; Yuan 2018	Minor allele → ↑ PSP risk; HIV neurocognitive impairment
EIF2AK3	rs6547787 (promoter)	Promoter SNP; in LD with haplotype B	Liu 2012 JBMR	Minor allele → ↓ BMD
EIF2AK3	rare biallelic LoF	Wolcott-Rallison syndrome (OMIM	Delépine 2000	Autosom

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
	(multiple)	226980): neonatal diabetes, epiphyseal dysplasia, growth retardation, hepatic dysfunction	Nat Genet; Senee 2004	al recessive ; ClinVar pathogen ic
ERN1 (IRE1α)	common SNPs poorly characterized	Splices XBP1 mRNA; required for UPR	Hetz 2020 Nat Rev Mol Cell Biol	Gene-region scan only
ATF6	rare biallelic LoF (multiple)	Achromatopsia type 7 (ACHM7); cone dystrophy	Kohl 2015 Nat Genet; ClinVar P/LP	Autosom al recessive ; very rare
XBP1	rs2269577 (-116 C>G, promoter)	Promoter; modest effect on XBP1 expression	Kakiuchi 2003; bipolar/IBD studies	Mixed; not strongly replicate d
DDIT3 (CHOP)	rs697221 (intronic)	Apoptotic UPR effector	Wang 2022 lung cancer	Risk allele → ↑ lung cancer in Chinese cohort
HSPA5 (BiP)	rs391957 (promoter)	ER master chaperone; sequesters PERK/IRE1/ATF6	Wang 2022	Promoter risk allele → ↑ lung cancer in Chinese cohort

Cofactors: ATP for PERK/IRE1 kinase activity; BiP requires ATP; Ca^{2+} homeostasis in the ER lumen depends on SERCA pumps and is essential for chaperone function. Practical levers: ISRIB (research compound) reverses PERK-dependent translation arrest; salubrinal stabilizes phospho-eIF2α; dietary restriction induces UPR resolution. Note: PERK-B haplotype increases ER-stress sensitivity but does not alter PERK basal activity (Ma et al., Sci Rep 2024 knock-in study).

3.5 Core autophagy machinery (initiation, conjugation, elongation)

Macroautophagy requires the ULK1 initiation complex, the BECN1/VPS34 nucleation complex, and two ubiquitin-like conjugation cascades (ATG12-ATG5-ATG16L1 and LC3-PE) that elongate the phagophore membrane. Loss of any core ATG component blocks autophagy. The most clinically replicated common variant in this category is ATG16L1 T300A, which weakens autophagy by enhancing caspase-3-mediated cleavage of ATG16L1 and is a robust GWAS-significant Crohn's risk allele in European populations.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
ATG7	rs36117895 (V471A, exon 14)	Nonsynonymous; impaired autophagy; modifier of HD age-of-onset (Italian cohort, not replicated in REGISTRY); NAFLD progression	Metzger 2013 PLoS ONE; Lee 2014 Hum Mol Genet (HD); Iorio 2024 Hepatology	C/Ala471 → ↑ NAFLD severity; HD-onset effect not robust
ATG7	rs143545741 (P426L)	Rare loss-of-function missense; impairs autophagy	Iorio 2024 Hepatology	Rare; ↑ NAFLD severity
ATG7	rs2447607 (intronic)	GWAS-significant for systolic blood pressure	Mátyás 2018 Sci Rep	Modest
ATG7	rs7635838 (intronic)	GWAS-significant for HDL	Mátyás 2018 Sci Rep ($p = 1.9\times10^{-9}$)	Modest
ATG16L1	rs2241880 (T300A, A>G, exon 9)	Nonsynonymous; T300A creates caspase-3 cleavage site; impairs xenophagy and unconventional autophagy; canonical mTOR-induced autophagy preserved	Hampe 2007 Nat Genet (CD GWAS); Murthy 2014 Nature; Lassen 2014 PNAS; Simovic 2024 UEG J meta-analysis	G/Ala300 → ↑ Crohn's risk OR 1.23 in Caucasians; ↑ perianal CD OR 1.21; mostly absent in East Asians
ATG16L1	rs10210302 (intron 5)	In strong LD with rs2241880	Same authors	Same direction
ATG16L1	rs1045100 (3'UTR)	In strong LD with rs2241880	Same authors	Same direction
ATG16L1	rs78835907	Tag SNP; prostate cancer recurrence in two independent cohorts	Liao 2015 Carcinogenesis	G allele → reduced PCa progression HR 0.70
ATG5	rs573775 (5'UTR), rs510432 (promoter), rs12201458	Promoter / 5'UTR; modulate ATG5 expression; childhood asthma association	Martin 2012 PLoS ONE	Risk alleles → ↑ asthma
BECN1	rs60221525, rs11552193	Common SNPs; modest cancer-outcome associations;	Choi 2024 review	Mostly somatic;

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
		haploinsufficient in 40-75% of breast/ovarian cancers somatically		germline effects modest
MAP1LC3B	common SNPs poorly characterized	Autophagosome marker; gene-region scan only	—	Speculative
MAP1LC3A	rs2424994	Intronic; modest CAD association	Mátyás 2018	Small
ULK1	rs11121704, rs1057079	Initiating kinase; modest AMD association	Wei 2020	Small

Cofactors: ATG7 is an E1-like enzyme using ATP. LC3 lipidation requires phosphatidylethanolamine (PE) on the autophagosome membrane. Polyamines (spermidine) induce autophagy through inhibition of EP300 acetyltransferase (Pietrocola Cell Death Differ 2015). Practical levers: rapamycin/sirolimus directly inhibits mTORC1; trehalose, spermidine, and resveratrol induce autophagy; dietary restriction and exercise potently induce autophagy via AMPK and TFEB.

3.6 Selective autophagy receptors and aggrephagy (SQSTM1/p62, OPTN)

Selective autophagy receptors bridge ubiquitinated cargo to LC3 on the autophagosome via UBA domains (cargo binding) and LIR motifs (LC3 binding). p62 (SQSTM1) is the canonical aggrephagy receptor and also bridges to KEAP1/Nrf2 oxidative stress signaling via its KIR motif. Mutations in SQSTM1 produce a multisystem proteinopathy spectrum with bone, motor neuron, frontotemporal cortex, and skeletal-muscle phenotypes.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
SQSTM1 (p62)	P392L (rare, c.1175C>T)	UBA domain; loss of K48 ubiquitin binding; classical Paget disease of bone (PDB)	Laurin 2002 Am J Hum Genet; Cavey 2006	Autosomal dominant; ClinVar pathogenic
SQSTM1	G411S, A381V, M404V, others — rare	UBA domain; PDB / Paget-spectrum	Multiple sources	Dominant; rare
SQSTM1	rare missense across LIR / KIR / TBS — multiple	ALS, FTD, FTD-ALS spectrum; LIR/KIR mutants disrupt liquid droplet formation, autophagy turnover, and Nrf2 activation	Le Ber 2013 JAMA Neurol; Fecto 2011 Arch Neurol; Kumar 2022 PMC8649403	Dominant; ALS-FTD continuum
SQSTM1	frameshift / truncating — rare	Distal myopathy with rimmed vacuoles; multisystem proteinopathy	Bucelli 2015 Neurology; Niu 2023 Front Neurol	Dominant; rare

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
SQSTM1	rs565280 (common)	Limited proteostasis association; AOSD candidate	Adult-onset Still's disease studies	Speculative
OPTN (Optineurin)	E478G, Q398X (rare)	Mitophagy receptor; ALS-FTD; primary open-angle glaucoma; PDB	Maruyama 2010 Nature; Rezaie 2002 Science	Dominant or recessive; rare
NBR1, TAX1BP1, NDP52 / CALCOCO2	common variants	Selective autophagy receptors; gene-region scans recommended	—	Mostly mechanistic

Cofactors: p62 phosphorylation by ULK1, CK2, and TBK1 regulates cargo binding. Practical levers: Nrf2 activators (sulforaphane, dimethyl fumarate) interact with the p62-KEAP1 axis; bisphosphonates and zoledronate are first-line for SQSTM1-associated Paget disease.

3.7 Mitophagy (PINK1, PRKN, PARK7) — cross-references PD report

PINK1 is a PTEN-induced kinase that accumulates on the outer membrane of depolarized mitochondria and recruits the cytoplasmic E3 ubiquitin ligase Parkin (encoded by PRKN), which ubiquitinates outer-membrane proteins, recruits p62 and OPTN, and drives mitochondrial clearance via autophagy. Rare biallelic LoF mutations in PINK1, PRKN, or PARK7 cause autosomal-recessive juvenile-onset Parkinson's disease. Common-variant effects are weaker but the gene region is included here for completeness with the broader PD panel.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
PINK1 (PARK6)	rare biallelic LoF (Q456X, others)	Mitochondrial kinase; loss of mitophagy initiation	Valente 2004 Science	Autosomal recessive juvenile PD; rare
PRKN (PARK2)	rare biallelic LoF, exonic deletions, multiplications	E3 ligase; loss of damaged-mitochondrion ubiquitination	Kitada 1998 Nature	Autosomal recessive juvenile PD; rare
PARK7 (DJ-1)	rare biallelic LoF (L166P, others)	Redox-sensitive chaperone; loss → mitochondrial dysfunction, oxidative stress	Bonifati 2003 Science	Autosomal recessive juvenile PD; rare

Cofactors: PINK1 requires ATP; Parkin uses ubiquitin and E2 enzymes; DJ-1 uses oxidatively-modified Cys106 as a redox sensor. Practical levers: NAD+ precursors (NMN, NR) support mitochondrial biogenesis; urolithin A induces mitophagy in muscle (Andreux Nature Metab 2019); exercise stimulates PGC-1α-driven mitochondrial turnover.

3.8 Lysosome and TFEB axis (TFEB, LAMP2, GBA1, VPS35)

The lysosome is the terminal degradative organelle, and its biogenesis and acidification capacity scale with cellular degradative demand through TFEB-driven CLEAR-network transcription. LAMP2 is the most abundant lysosomal membrane protein (with three splice isoforms; LAMP2A is the CMA receptor). GBA1 hydrolyses glucosylceramide. Retromer (VPS35-VPS26-VPS29) recycles transmembrane receptors from endosomes to TGN/PM.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
TFEB	common functional SNPs sparse	Master regulator; somatic translocations in renal cancers	Settembre 2011 Science; Sardiello 2009 Science; Takla 2023 EMBO Rep	Gene-region scan only
LAMP2	rare LoF (multiple)	Danon disease (X-linked dominant): hypertrophic cardiomyopathy, skeletal myopathy, intellectual disability; LAMP2A loss → CMA failure	Nishino 2000 Nature; Taylor 2007	X-linked; ClinVar pathogenic; rare
GBA1	rs76763715 (N370S, exon 9)	Mild GD-causing variant; ~7-38% residual GCase activity	Beutler 1991 PNAS; Sidransky 2009 NEJM (PD)	Heterozygous → ↑ PD OR ~3-5; cross-ref PD report
GBA1	rs2230288 (E326K / E365K)	Risk variant (does not cause GD); near-wildtype enzymatic activity but disrupts LIMP2 binding, drives α-syn aggregation and lipid droplet accumulation	Mata 2008; Duran 2013; Hu 2025 bioRxiv	Heterozygous → ↑ PD OR 1.57-5.50, ↑ DLB; ↑ rapid cognitive decline
GBA1	rs75548401 (T369M)	Risk variant (mild)	Lwin 2004; Mallett 2016	Heterozygous → ↑ PD OR ~1.3-2
GBA1	rs421016 (L444P, exon 10)	Severe GD-causing variant; ~13-24% residual activity	Tsuji 1987 NEJM; Sidransky 2009	Heterozygous → ↑ PD OR ~5-10; cross-ref PD report
VPS35	rs188286943 (D620N)	Retromer; D620N reduces WASH complex association; impairs autophagy; enhances LRRK2 kinase activity	Vilarino-Güell 2011 Am J Hum Genet; Williams 2017; McCarron	Autosomal dominant late-

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
			2024 BCJ	onset PD; ClinVar pathogenic; cross-ref PD report
CTSD (cathepsin D)	rare LoF	Lysosomal aspartyl protease; CLN10 neuronal ceroid lipofuscinosis when biallelic	Siintola 2006 Brain	Autosomal recessive; very rare

Cofactors: lysosomal hydrolases require acid pH (~4.5) maintained by V-ATPase; GCase requires saposin C (PSAP-derived) and LIMP2 for lysosomal delivery. Practical levers: ambroxol (an OTC mucolytic in many countries) functions as a pharmacological chaperone for GCase and is in clinical trials for GBA-PD (Mullin Mov Disord 2020); chloroquine/HCQ raise lysosomal pH (used immunomodulatorily); nicotinamide riboside / NMN may support lysosomal function via SIRT1; exercise induces TFEB nuclear translocation in skeletal muscle (Mansueto Cell Metab 2017).

3.9 Master regulators (FOXO3, SIRT1, mTOR)

Three upstream regulators integrate nutrient, energy, and stress signals into proteostasis output. mTORC1 phosphorylates TFEB and ULK1 to suppress autophagy under nutrient-replete conditions; AMPK opposes mTORC1 to promote autophagy under energy stress. FOXO3 is downstream of insulin/IGF-1/Akt and drives expression of autophagy and stress-resistance genes. SIRT1 is an NAD+-dependent deacetylase that activates HSF1 and FOXO3 and links nutrient state to proteostasis. The FOXO3 longevity SNP rs2802292 directly couples HSF1 binding to FOXO3 transcription, providing a molecular link between heat-shock response and autophagy / longevity.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
FOXO3	rs2802292 (intron 2, T>G)	G allele creates an HSF1 binding site in an intronic enhancer; HSF1 binding induces FOXO3 expression under stress	Willcox 2008 PNAS; Donlon 2018 NAR; Bao 2024 npj Aging	G/ longevity allele → ~1.9× probability of reaching age 95 (p = 0.0003)
FOXO3	rs2802288, rs768023, rs2253310, rs13217795	Tag SNPs in LD with rs2802292; longevity haplotype	Flachsbart 2009 PNAS; Anselmi 2009 Rejuvenation Res; Chen 2018	Same direction; replicated in European, East

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
				Asian, Italian centenarians, Ashkenazi Jews
SIRT1	rs7895833, rs7069102, rs2273773	NAD+-dependent deacetylase; deacetylates HSF1, FOXO3, p53, NF-κB	Several metabolic / longevity studies	Mixed evidence; effect sizes modest
MTOR	rs2295080 (-104 C>A, promoter)	Promoter; alters mTOR expression	Wei 2020 wet AMD; Slattery 2010 cancer	Risk allele → ↑ wet AMD; ↑ some cancer outcomes
MTOR	rs1057079, rs11121704	Intronic / 3'UTR; AMD risk modifiers	Wei 2020	Modest
AMPK (PRKAA2)	rs10789038, rs2796516	Energy-sensing kinase; opposes mTORC1	T2D / metabolic studies	Modest

Cofactors: SIRT1 requires NAD+. AMPK is activated by AMP and metformin/biguanides. mTOR is inhibited by rapamycin/sirolimus and everolimus. Practical levers: dietary restriction, time-restricted eating, exercise, metformin, NAD+ precursors (NR/NMN), spermidine, and rapamycin all converge on these regulators (Madeo Nat Rev Drug Discov 2019). The FOXO3 G-allele effect is preserved across populations; the longevity benefit appears to operate through HSF1-driven FOXO3-driven SOD2/CAT/GADD45A/autophagy gene expression.

4. Variant Lookup Table (master rsID list)

Single-SNP panel variants used for the call-rate denominator; gene regions for rare-variant scanning are listed separately in §5.

rsID	Gene	Variant	Functional consequence	ClinVar
rs1043618	HSPA1A	5'UTR +190 G>C	↓ HSP70 translation efficiency in C carriers	—
rs1008438	HSPA1A	-110 A>C promoter	Reduced promoter activity in C carriers	—
rs2227956	HSPA1L	T493M	Substrate-binding domain Thr→Met	—
rs2075800	HSPA1L	E272K	NBD-SBD linker Glu→Lys	—

rsID	Gene	Variant	Functional consequence	ClinVar
rs1061581	HSPA1B	Q351Q (synonymous)	Tag for regulatory haplotype	—
rs2763979	HSPA1B	5' regulatory	Modulates basal HSP70 expression	—
rs391957	HSPA5 (BiP)	promoter	ER chaperone expression	—
rs430397	HSPA5	promoter	Modulates BiP expression	—
rs36117895	ATG7	V471A	Mild loss-of-function; impaired autophagy	Conflicting
rs143545741	ATG7	P426L	Rare loss-of-function	Likely pathogenic for NAFLD
rs2447607	ATG7	intronic	GWAS systolic BP / pulse pressure	—
rs7635838	ATG7	intronic	GWAS HDL	—
rs2241880	ATG16L1	T300A	Caspase-3 cleavage site; impaired xenophagy	Risk factor (CD)
rs78835907	ATG16L1	intronic	Prostate cancer outcome modifier	—
rs60221525	BECN1	common SNP	Modest cancer-outcome	—
rs11552193	BECN1	common SNP	Modest cancer-outcome	—
rs2295080	MTOR	-104 C>A promoter	Modulates mTOR expression	—
rs10902469	MTOR	intronic	AMD risk modifier	—
rs7310501 3	MTOR	intronic	Wet AMD risk modifier	—
rs1057079	MTOR	3'UTR	AMD risk modifier	—
rs11121704	MTOR	intronic	AMD risk modifier	—
rs573775	ATG5	5'UTR	ATG5 expression / asthma	—
rs11246867	ULK1	intronic	Initiating kinase; modest AMD	—

rsID	Gene	Variant	Functional consequence	ClinVar
rs3088051	SQSTM1	intronic	AOSD candidate	—
rs10277	SQSTM1	tag SNP	AOSD candidate	—
rs13045	EIF2AK3	Q166R / R166Q	PERK haplotype B coding tag	—
rs867529	EIF2AK3	S136C	PERK haplotype B coding tag	—
rs1805165	EIF2AK3	S704A / A704S	PERK haplotype B coding tag	—
rs7571971	EIF2AK3	intron 2	GWAS-significant PSP risk haplotype	Risk factor (PSP)
rs6547787	EIF2AK3	promoter	Haplotype B promoter SNP	—
rs2269577	XBP1	-116 C>G	Promoter modulation	—
rs2802292	FOXO3	intron 2	Creates HSF1 binding site; longevity	—
rs2802288	FOXO3	intronic	Tag for longevity haplotype	—
rs7895833	SIRT1	promoter region	Modest metabolic effects	—
rs7069102	SIRT1	intronic	Modest metabolic effects	—
rs76763715	GBA1	N370S	Mild GD; PD risk	Pathogenic (GD); risk (PD)
rs2230288	GBA1	E326K	PD risk variant; α-syn aggregation	Risk factor (PD)
rs75548401	GBA1	T369M	Mild PD risk variant	Risk factor (PD)
rs421016	GBA1	L444P	Severe GD; PD risk	Pathogenic (GD); risk (PD)
rs188286943	VPS35	D620N	Retromer; ↑ LRRK2 kinase; ↓ autophagy	Pathogenic (PD)
rs34637584	LRRK2	G2019S	Kinase domain; ↑ activity (cross-ref PD)	Pathogenic (PD)
rs76904798	LRRK2	5' regulatory (cross-ref PD)	Modest PD risk	Risk factor

rsID	Gene	Variant	Functional consequence	ClinVar
rs356182	SNCA	(cross-ref PD)	α-synuclein expression modifier	Risk factor
rs1052553	MAPT	(cross-ref PD)	H1/H2 haplotype tag	Risk factor
rs6721961	NFE2L2	(cross-ref PD)	Nrf2 promoter; oxidative stress response	—
rs387907571	DNAJC13	N855S	Originally PD-linked; not replicated 2025	Conflicting

5. Gene Regions Scanned

The Phase 3 query script scans the following gene regions for rare or uncatalogued variants. Region names ending in _full_region or _region are excluded from the single-SNP call-rate denominator.

Gene	Coordinates (GRCh38)	Rationale
HSPA1A	chr6:31815343-31817862	Common HSP70 inducible isoform; HLA class III
HSPA1B	chr6:31828300-31830720	Tandem duplicate of HSPA1A
HSPA1L	chr6:31810400-31816000	Constitutive HSP70-like
HSPA5 (BiP)	chr9:125887000-125925000	ER UPR master chaperone
HSF1	chr8:144511000-144516000	Master HSR transcription factor
HSPB1 (HSP27)	chr7:75932000-75934000	CMT2F / dHMN2 dominant alleles
CRYAB	chr11:111777000-111780000	Myofibrillar myopathy + cataract
EIF2AK3 (PERK)	chr2:88556741-88691518	Wolcott-Rallison; PSP haplotype B
ERN1	chr17:33223000-33267000	UPR sensor;

Gene	Coordinates (GRCh38)	Rationale
(IRE1α)		XBP1 splicing
ATF6	chr1:161516000-161558000	UPR sensor; ACHM7 when biallelic
XBP1	chr22:28794000-28800000	UPR transcription factor
DDIT3 (CHOP)	chr12:57231000-57243000	Apoptotic UPR effector
ATF4	chr22:39520000-39524000	ISR transcription factor
ATG7	chr3:11279000-11430000	E1-like; NAFLD progression alleles
ATG16L1	chr2:233214000-233303000	T300A in WD40 / coiled-coil
ATG5	chr6:106534000-106562000	Conjugation partner of ATG12
BECN1	chr11:119089000-119223000	Class III PI3K nucleator
MAP1LC3B	chr16:16996000-17042000	Autophagosome marker
ULK1	chr12:131891000-131909000	Initiating kinase
SQSTM1 (p62)	chr5:179806000-179838000	PDB / ALS-FTD / DMRV alleles
OPTN	chr10:60771000-60891000	ALS-FTD / glaucoma / PDB
DNAJB1	chr19:36210000-36218000	Cytosolic HSP40
DNAJB6	chr7:157129000-157203000	α-syn / polyQ aggregation suppressor; LGMDD1
DNAJC6 (auxilin-1)	chr1:65343000-65455000	PARK19 (juvenile

Gene	Coordinates (GRCh38)	Rationale
		recessive PD)
DNAJC13 (RME-8)	chr3:132165000-132295000	Autophagic lysosome reformation
GBA1	chr1:155234451-155244699	Cross-ref PD report
VPS35	chr16:46693060-46723175	Retromer; D620N in PD
PINK1	chr1:20633598-20651709	Cross-ref PD report
PRKN	chr6:161347417-162727802	Cross-ref PD report
PARK7 (DJ-1)	chr1:7954290-8043800	Cross-ref PD report
LAMP2	chrX:120431000-120470000	Danon disease (X-linked); LAMP2A is CMA receptor
TFEB	chr6:41651000-41714000	Master regulator
CTSD	chr11:1752000-1768000	Lysosomal protease; CLN10 when biallelic
FOXO3	chr6:108881000-109006000	Longevity locus
SIRT1	chr10:67884000-67918000	NAD+-dependent deacetylase
MTOR	chr1:11106000-11264000	Master autophagy inhibitor

6. Functional Categories → Cofactors → Supplement / Lifestyle Targets

Category	Genes	Cofactors / substrates	Supplement / lifestyle targets
Cytosolic chaperones / HSR	HSPA1A/B/L, HSPA8, HSF1	ATP, Mg^{2+}, NAD+ (for SIRT1-HSF1 deacetylation)	Sauna / heat exposure (HSF1 induction); endurance exercise;

Category	Genes	Cofactors / substrates	Supplement / lifestyle targets
			NAD+ precursors (NR / NMN); short-term fasting
Small HSPs	HSPB1, HSPB8, CRYAB	ATP-independent (oligomeric state regulated by p38-MK2)	Heat exposure; endurance training
DNAJ co-chaperones	DNAJB6, DNAJC6, DNAJC13	ATP via HSP70 cycle	(no direct supplement); urolithin A may help mitophagy-coupled DNAJ
UPR (ER stress)	EIF2AK3, ERN1, ATF6, HSPA5, XBP1, DDIT3	ATP for kinases; Ca^{2+} in ER lumen	ISRIB (research); salubrinal (research); dietary restriction; avoid chronic ER lipid stress (saturated fat / fructose excess)
Core autophagy	ATG7, ATG16L1, ATG5, BECN1, MAP1LC3B, ULK1	ATP for ATG7 E1; phosphatidylethanolamine for LC3 lipidation	Spermidine; trehalose; rapamycin / sirolimus (mTOR); resveratrol; metformin; exercise; intermittent / time-restricted eating
Selective autophagy	SQSTM1, OPTN, NBR1	Ubiquitin chains; LC3-PE	Sulforaphane (Nrf2 / KEAP1 axis); dimethyl fumarate
Mitophagy	PINK1, PRKN, PARK7	ATP; ubiquitin; oxidatively-modified Cys106 in DJ-1	Urolithin A; NAD+ precursors; exercise (PGC-1α)
Lysosome / TFEB	TFEB, LAMP2, GBA1, VPS35, CTSD	Acid pH (V-ATPase); LIMP2 for GCase delivery; saposin C	Ambroxol (GCase chaperone — cross-ref PD); exercise (TFEB nuclear translocation); avoid lysosome-disrupting drugs
Master regulators	FOXO3, SIRT1, MTOR, AMPK	NAD+ for SIRT1; AMP for AMPK	NAD+ precursors; metformin; rapamycin; dietary restriction; resveratrol; spermidine

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