Rapamycin / mTOR Pathway Genetic Pathway Reference

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11 Functional Categories • ~70 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of the mechanistic target of rapamycin (mTOR) signaling network, the genes that regulate each node of the pathway, the well-studied common variants in those genes, the cofactors each enzyme or signaling component depends on, and the supplement, dietary, and pharmacologic targets that map to each cofactor and pathway. It is intended for use by clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on published GWAS literature, peer-reviewed mechanistic studies, and pharmacogenomic consortia (CPIC, PharmGKB). The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations. Most common variants catalogued here confer small individual effects (per-allele odds ratios 1.1 to 1.5); clinical significance arises from cumulative patterns and gene-pharmacology interactions. A small number of variants — notably CYP3A5*3 (rs776746) for sirolimus pharmacokinetics, MTOR rs2295080, IRS1 rs2943641, FKBP5 rs1360780, FOXO3 rs2802292, and the rare loss-of-function mutations in TSC1, TSC2, STK11, and PTEN — have larger and clinically actionable effect sizes.

2. Pathway Biology

2.1 What mTOR is and why it matters

Mechanistic (formerly mammalian) target of rapamycin, mTOR, is an atypical Ser/Thr kinase of the phosphatidylinositol-3-kinase-related kinase (PIKK) family. It is the master integrator of cellular nutrient, growth-factor, energy, and stress signals, and is among the most evolutionarily conserved regulators of cell growth, metabolism, and longevity (Liu and Sabatini, Nat Rev Mol Cell Biol 2020; Saxton and Sabatini, Cell 2017). mTOR functions in two structurally and functionally distinct complexes — mTORC1 and mTORC2 — that share the kinase itself and a small accessory subunit (mLST8, gene MLST8) plus the negative regulator DEPTOR, but differ in their defining partners and in their sensitivity to rapamycin.

2.2 mTORC1 — the rapamycin-sensitive anabolic complex

mTORC1 contains mTOR, Raptor (RPTOR), mLST8, the inhibitor PRAS40 (AKT1S1), and DEPTOR. Raptor recruits substrates by recognizing TOR-signaling (TOS) motifs. mTORC1 is recruited to the lysosomal surface by amino acids (via the Rag GTPase heterodimer and the Ragulator complex) and is activated there by Rheb-GTP, whose GTP loading is controlled by the TSC1-TSC2 GTPase-activating protein complex. The four canonical inputs converging on

mTORC1 are: (1) growth factors (insulin and IGF-1) acting through PI3K-AKT-TSC2; (2) amino acids — especially leucine, arginine, and methionine — acting through Sestrin2, CASTOR1, and SAMTOR onto the Rag GTPases; (3) cellular energy — high AMP/ATP ratio acting through LKB1-AMPK to phosphorylate TSC2 and Raptor; and (4) stress signals — hypoxia (REDD1/DDIT4), DNA damage (ATM), and ER stress acting through TSC2.

Active mTORC1 phosphorylates two principal classes of substrates that drive anabolism: ribosomal protein S6 kinase 1 (S6K1, encoded by RPS6KB1), which activates mRNA translation; and 4E-BP1 (encoded by EIF4EBP1), whose phosphorylation releases the cap-binding factor eIF4E to initiate cap-dependent translation. Beyond translation, mTORC1 activates lipid synthesis through SREBP1 and SREBP2 (Porstmann, Cell Metab 2008), promotes nucleotide biosynthesis, increases mitochondrial biogenesis, and shuts off autophagy by phosphorylating ULK1 and TFEB.

2.3 mTORC2 — the rapamycin-mostly-insensitive cytoskeletal and AKT complex

mTORC2 contains mTOR, Rictor, mSIN1 (MAPKAP1), Protor 1/2 (PRR5, PRR5L), mLST8, and DEPTOR. Rictor and mSIN1 sterically prevent FKBP12-rapamycin from docking, which is why acute rapamycin does not inhibit mTORC2. mTORC2 phosphorylates the AGC kinase family at hydrophobic-motif sites — most importantly AKT at Ser473, plus SGK1 at Ser422 and conventional and novel PKC isoforms (Sarbassov, Science 2005). AKT Ser473 phosphorylation, working with PDK1-mediated Thr308 phosphorylation, is required for full AKT activation and for AKT's ability to suppress FOXO transcription factors.

In liver, mTORC2 is essential for full insulin-stimulated AKT activation. Loss of hepatic mTORC2 function uncouples insulin signaling from glucose homeostasis: FOXO1 is no longer fully suppressed, and the gluconeogenic program (G6PC, PCK1) remains active in the fed state. This is the molecular basis of rapamycin-induced glucose intolerance (Lamming, Science 2012; Houde, Diabetes 2010).

2.4 How rapamycin works at the molecular level

Rapamycin (sirolimus) is a macrolide produced by Streptomyces hygroscopicus. It crosses cell membranes and binds the small immunophilin FKBP12 (encoded by FKBP1A). The FKBP12-rapamycin complex docks onto the FRB (FKBP-rapamycin binding) domain of mTOR within mTORC1, allosterically inhibiting kinase activity by partially obstructing the substrate-binding cleft (Choi, Science 1996; Yang, Nature 2013). S6K1 phosphorylation collapses within minutes of exposure; 4E-BP1 phosphorylation is more resistant, particularly at the priming sites (Choo, PNAS 2008; Kang, Science 2013). The clinical analogs everolimus, temsirolimus, and ridaforolimus share this mechanism with minor pharmacokinetic differences.

mTORC2 is acutely insensitive because Rictor blocks FKBP12-rapamycin docking. However, prolonged rapamycin exposure progressively inhibits mTORC2 because rapamycin binds and sequesters newly synthesized mTOR before it can assemble into mTORC2; mTORC1 reassembles unaffected because Raptor-mTOR association is faster (Sarbassov, Mol Cell 2006). The half-life of mTORC2 disassembly varies by tissue — adipose and liver are more sensitive than skeletal muscle. This dissociation kinetics is the rationale for intermittent (weekly or longer-interval) rapamycin dosing in longevity protocols, which preserves mTORC1 inhibition while allowing mTORC2 to reassemble between doses (Arriola Apelo, J Gerontol A 2016; Bitto, eLife 2016; Mannick, Sci Transl Med 2014).

2.5 Why mTOR matters for aging and longevity

Reduced mTOR signaling extends lifespan in every model organism tested — yeast, worms, flies, and mice (Vellai, Nature 2003; Kapahi, Curr Biol 2004; Kaeberlein, Science 2005; Harrison, Nature 2009; Miller, Aging Cell 2014). The NIH Interventions Testing Program has reproducibly shown rapamycin extension of mouse lifespan across genetic backgrounds and dosing schedules, with effects of approximately 10 to 25 percent on median and maximum lifespan. Mechanisms include increased autophagy and proteostasis, FOXO3 activation (with subsequent transcription of antioxidant and DNA-repair genes), reduced senescence-associated secretory phenotype, attenuated IGF-1 signaling, improved mitochondrial quality control, and improved immune function in aged organisms. mTOR is uniquely positioned as the pharmacologically tractable node of the nutrient-sensing arm of the hallmarks-of-aging framework (López-Otín, Cell 2013, 2023).

2.6 Rapamycin's metabolic side effects: glucose and lipids

Two classes of metabolic side effects are reproducibly seen with chronic rapamycin: glucose intolerance and dyslipidemia. Both are largely attributable to mTORC2 inhibition rather than to mTORC1 inhibition itself.

The glucose effect operates principally through hepatic mTORC2 loss. Reduced mTORC2 activity in hepatocytes lowers AKT Ser473 phosphorylation, which fails to suppress nuclear FOXO1, which then drives transcription of G6PC (glucose-6-phosphatase) and PCK1 (PEPCK), increasing hepatic gluconeogenesis and producing fasting hyperglycemia (Lamming, Science 2012; Hagiwara, Cell Metab 2012). In parallel, adipose mTORC2 inhibition impairs lipid storage and pushes free fatty acids into circulation, producing peripheral lipotoxicity and insulin resistance (Kumar, Diabetes 2010; Cybulski, PNAS 2009). At very high chronic doses, beta-cell mTORC1 inhibition modestly blunts insulin secretion as well (Fraenkel, Diabetes 2008). At intermittent longevity-style dosing the blood-glucose effect is much smaller but mechanistically present.

The lipid effect — raised triglycerides and LDL cholesterol — occurs through mTORC1's regulation of SREBP1 and SREBP2 in liver, plus altered lipoprotein lipase regulation and modestly reduced LDL clearance. The mechanism is incompletely understood but the phenotype is reproducible across transplant cohorts on continuous sirolimus, where new-onset hyperlipidemia incidence approaches 30 to 45 percent (Morrisett, J Lipid Res 2002; Brattstrom, Transplantation 1998). At intermittent dosing the lipid effect is less prominent but is the most common clinically observed change.

2.7 Strategies for selective mTORC1 inhibition

Because mTORC1 inhibition mediates rapamycin's longevity benefit while mTORC2 inhibition mediates its metabolic side effects, there is sustained interest in selectively inhibiting mTORC1 while sparing mTORC2. Four general strategies are recognized in the literature.

First, intermittent dosing. Weekly or biweekly rapamycin produces near-equivalent mTORC1 inhibition compared with daily dosing while allowing mTORC2 to reassemble between doses (Arriola Apelo, J Gerontol A 2016). The PEARL trial of weekly rapamycin in healthy adults showed measurable changes in body composition without glucose disturbance (Kaeberlein, Aging Cell 2023, in adult cohort).

Second, dose reduction. Lower trough levels stay within the mTORC1-selective window — mTORC1 has a meaningfully lower IC50 than the threshold for sustained mTORC2 disassembly (Schreiber, Aging Cell 2015). Trough levels of 5 to 10 ng/mL for sirolimus are typically cited for

longevity use, well below the 8 to 15 ng/mL transplant range that produces the metabolic phenotype.

Third, third-generation rapalogs designed for mTORC1-selectivity. Bivalent compounds such as RMC-5552 and RMC-6272 use ternary FKBP12-drug-mTOR complex geometries that prefer Raptor-bound mTORC1 over Rictor-bound mTORC2 (Lee, Cancer Discov 2021). These are in oncology trials but not in routine longevity practice.

Fourth, combination with AMPK activators or growth-factor reducers. Co-administration of metformin or imeglimin (AMPK activation, TSC2 phosphorylation), GLP-1 receptor agonists (reduced hyperinsulinemia), or caloric/protein restriction reduces total mTOR signaling drive, allowing equivalent functional mTORC1 inhibition at lower rapamycin doses. Rapamycin plus metformin in mice produces lifespan extension equivalent to rapamycin alone but with reduced glucose intolerance (Strong, Aging Cell 2016).

3. Functional Categories

The rapamycin / mTOR pathway is organized into eleven functional categories. The categories are used as the organizing scaffold for the SNP catalog in Section 4.

#	Category	Function	Key genes
1	Drug pharmacokinetics	Rapamycin absorption, metabolism, transport	CYP3A4, CYP3A5, ABCB1, SLCO1B1
2	Immunophilins / drug binding	FKBP family proteins binding rapamycin	FKBP1A, FKBP5, FKBP4
3	mTOR catalytic core	Kinase and complex-defining subunits	MTOR, RPTOR, RICTOR, MLST8, MAPKAP1
4	PI3K / AKT input arm	Insulin and IGF-1 signal transduction to mTOR	PIK3CA, PIK3R1, AKT1, AKT2, PTEN, IRS1, IRS2
5	TSC / Rheb central rheostat	Integration of inputs onto mTORC1 via Rheb-GTP	TSC1, TSC2, RHEB
6	Energy sensing (AMPK / LKB1)	Low-energy signal to inhibit mTORC1	STK11, PRKAA1, PRKAA2, PRKAB1, PRKAG2
7	Amino acid sensing (Rag axis)	Lysosomal mTORC1 recruitment by amino acids	RRAGA, RRAGC, SESN2, CASTOR1
8	Translation effectors	Anabolic output from active mTORC1	RPS6KB1, EIF4EBP1, EIF4E
9	Lipogenesis effectors	Lipid and cholesterol synthesis (rapamycin lipid side effect)	SREBF1, SREBF2, MLXIPL, INSIG2
10	FOXO / autophagy / longevity	Downstream longevity and autophagy outputs	FOXO1, FOXO3, ULK1, ATG7, GSK3B
11	Rapamycin glucose dysregulation	Hepatic gluconeogenesis and peripheral GLUT4 (mTORC2 side effect)	G6PC, G6PC2, PCK1, FOXO1, RICTOR, MAPKAP1, AKT2, TBC1D4, SLC2A4, IRS1, GCKR, CRTC2, PRKAA2, PPP1R3A

4. SNP Catalog by Functional Category

Each table below lists the well-studied common variants in the genes for that category, along with the variant name, the functional consequence, and the cofactor or pathway node required by the associated protein. Effect sizes and GWAS p-values are noted where well established. Each table is followed by an italicized summary of what the category represents biologically.

4.1 Drug pharmacokinetics

Gene	rsID	Variant	Functional consequence	Cofactor / node
CYP3A5	rs776746	*3 (6986A>G)	Splice defect; G allele carriers have no functional CYP3A5 (>90% Europeans). ~30% reduction in sirolimus clearance (Anglicheau, J Am Soc Nephrol 2003).	NADPH, O_2
CYP3A4	rs35599367	*22 (intron 6 C>T)	T allele reduces CYP3A4 expression ~50%; lower sirolimus clearance, higher AUC (Wang, Pharmacogenomics J 2011).	NADPH, O_2
CYP3A4	rs2740574	*1B (-392A>G)	Promoter variant in LD with *22 in some haplotypes; modest reduction in CYP3A4 activity.	NADPH, O_2
ABCB1	rs1045642	C3435T (silent)	Affects mRNA folding/stability; mixed effect on rapamycin AUC.	ATP
ABCB1	rs1128503	C1236T	Haplotype tag; co-inherited with rs1045642 and rs2032582.	ATP
SLCO1B1	rs4149056	*5 (Val174Ala)	Reduced OATP1B1 hepatic uptake; sirolimus is a substrate. C/C ~2-3x higher exposure for some substrates (CPIC level A for statins).	Bicarbonate, GSH gradient

*This category determines individual rapamycin exposure at a given oral dose. Sirolimus is metabolized primarily by CYP3A4 and CYP3A5 in liver and intestine; CYP3A5*3/*3 non-expresser status (the European norm) and CYP3A4*22 carrier status both predict lower clearance and higher AUC. Concomitant CYP3A inhibitors (clarithromycin, ketoconazole, voriconazole, diltiazem, grapefruit juice) further raise exposure; inducers (rifampin, St John's wort, modafinil, carbamazepine) lower it. From an mTORC1-selective perspective, longer drug exposure per dose pushes slightly toward more mTORC2 effect.*

4.2 Immunophilins / drug binding

Gene	rsID	Variant	Functional consequence	Cofactor / node
FKBP1A	rs6041749	3' UTR	FKBP12 is the obligate immunophilin partner for rapamycin. Common variants poorly characterized for clinical effect; rare LoF would abolish rapamycin activity (Stocco, Pharmacogenomics J 2017).	PPIase activity

Gene	rsID	Variant	Functional consequence	Cofactor / node
FKBP5	rs1360780	intronic C>T	T allele increases FKBP5 expression, desensitizing the glucocorticoid receptor; modulates stress axis and mTOR-mediated insulin resistance (Binder, Nat Genet 2004; Klengel, Nat Neurosci 2013).	GR cochaperone
FKBP5	rs3800373	3' UTR	T allele tags the same risk haplotype as rs1360780 (Binder, Nat Genet 2004).	GR cochaperone
FKBP4	rs1565445	intronic	FKBP52, regulates AR/GR. Limited rapamycin-specific data; theoretical relevance to AR-driven prostate biology (Storer, Endocr Rev 2011).	AR/GR cochaperone

FKBP12 (FKBP1A) is the small immunophilin that binds rapamycin and forms the inhibitory complex with mTOR. Common variation in FKBP1A is poorly studied genetically — its function is so essential that loss-of-function would be incompatible with rapamycin response. FKBP5 is more polymorphic and clinically actionable; its expression level affects glucocorticoid receptor sensitivity and indirectly modulates mTOR-mediated metabolic effects, with the T allele at rs1360780 (the most-studied variant) creating an epigenetic feedback loop with childhood adversity that has been replicated in dozens of psychiatric and metabolic cohorts.

4.3 mTOR catalytic core

Gene	rsID	Variant	Functional consequence	Cofactor / node
MTOR	rs2295080	promoter T>G	T allele in transcription factor binding site; T/T homozygotes show higher mTOR mRNA (gastric, renal, colorectal). Associated with differential sirolimus response in transplant cohorts (He, PLoS One 2013; Cao, PLoS One 2012; Wu, Pharmacogenomics 2015).	ATP, Mg^{2+}
MTOR	rs1883965	intronic G>A	Heterozygote-risk pattern; meta-analysis OR 1.15 for cancer (Zining, Sci Rep 2017, 23 studies).	ATP, Mg^{2+}
MTOR	rs2536	3'-UTR T>C	miRNA-binding-site variant; alters miR-767-3p regulation (Li, Mol Carcinog 2013).	ATP, Mg^{2+}
MTOR	rs1034528	intronic G>C	Heterozygote OR 1.30 for cancer in meta-analysis (Zining, 2017).	ATP, Mg^{2+}
MTOR	rs17036508	intronic T>C	Heterozygote OR 1.23 for cancer; lower mTOR transcript in HapMap (Zining, 2017).	ATP, Mg^{2+}
RPTOR	rs1468033	intronic A>G	Modifies prostate cancer risk in	Raptor

Gene	rsID	Variant	Functional consequence	Cofactor / node
			subgroups defined by age, BMI, smoking (Chen, Cancer 2013).	scaffold
RICTOR	rs2043112	intronic	Modulates mTORC2 activity; limited replication.	Rictor scaffold
MAPKAP1	rs7211818	intronic	mSIN1 expression modifier; sparse data.	mSIN1 PH domain
MLST8	rs3736984	intronic	Shared core subunit; limited population data.	GβL scaffold

This category is the catalytic and scaffold core of both mTOR complexes. The most-studied single variant is MTOR rs2295080, a promoter T/G polymorphism in a transcription factor binding site; the T allele increases mTOR transcription in multiple tissues. Direction of effect on rapamycin response is uncertain in the literature, but a higher baseline mTOR transcript pool plausibly means more substrate available for FKBP12-rapamycin engagement. Common variants in RPTOR, RICTOR, MAPKAP1, and MLST8 are less well characterized; rare RICTOR amplifications occur in cancer.

4.4 PI3K / AKT input arm

Gene	rsID	Variant	Functional consequence	Cofactor / node
PIK3CA	rs2699887	intronic A>G	Modulates platinum chemotherapy toxicity, lung cancer outcomes (Pu, Carcinogenesis 2011).	ATP, PIP2
PIK3CA	rs6443624	intronic C>A	A allele protective for bladder cancer (Tabone, Mol Med Rep 2018).	ATP, PIP2
AKT1	rs1130214	5' UTR G>T	Tag SNP for AKT1 expression. T allele associated with reduced PDK1 and AKT1 activity, better cancer outcomes (HR 0.62 for distant progression; Kim, Pharmacogenet Genomics 2008; Pu, Carcinogenesis 2010).	ATP, Mg^{2+}
AKT1	rs2494752	promoter A>G	G allele increases AKT1 promoter activity; breast and gastric cancer risk (Wang, Sci Rep 2016).	ATP, Mg^{2+}
AKT1	rs1130233	exon synonymous A>G	Bladder cancer risk in homozygotes OR 5.81 (Tabone, 2018).	ATP, Mg^{2+}
PTEN	rs701848	3' UTR T>C	C allele in miRNA binding site, reduces PTEN, raises PI3K/AKT signaling. CC OR 1.17 for cancer; modulates antiepileptic response (Song, Oncotarget 2017).	PIP3 phosphatase
PTEN	rs2735343	promoter G>C	GG genotype increases cancer risk in	PIP3

Gene	rsID	Variant	Functional consequence	Cofactor / node
			dominant model (Song, 2017).	phosphatase
IRS1	rs2943641	near-IRS1 C>T	C allele protective: enhances IRS1 signaling, reduces T2D risk; protects against mTORC1-S6K1-IRS1 negative-feedback insulin resistance (Rung, Nat Genet 2009; n>50,000).	tyrosine phosphorylation
IRS2	rs1865434	intronic	Modest T2D risk modifier (Bonnefond, Diabetes 2008).	tyrosine phosphorylation

This category transduces growth-factor signals (insulin, IGF-1) into mTORC1 activation. AKT phosphorylates TSC2 (inhibiting it, releasing Rheb-GTP) and PRAS40 (releasing mTORC1). PTEN counterbalances PI3K by dephosphorylating PIP3. The IRS1 rs2943641 protective C allele is one of the largest-effect insulin-sensitivity variants in the GWAS catalog and is particularly important under chronic mTOR inhibition because it counteracts the S6K1→IRS1 Ser1101 negative-feedback loop that otherwise causes mTORC1-driven insulin resistance.

4.5 TSC / Rheb central rheostat

Gene	rsID	Variant	Functional consequence	Cofactor / node
TSC1	rs7874234	intronic	TT carriers have 9-year-later age at ER+ breast cancer diagnosis; T allele may create estrogen-responsive element (Mehta, Breast Cancer Res Treat 2011).	TSC2 binding
TSC1	rs2809244	intronic	Tag SNP from haplotype mapping (Mehta, 2011).	TSC2 binding
TSC2	rs2073869	intronic	Tag SNP; limited functional data.	Rheb GAP
TSC2	rs45517223 (rare)	M286V	Disrupts TSC1 binding in mouse model → hepatic steatosis (Mensenkamp, Diabetes 2012).	Rheb GAP
RHEB	rs375697977 (rare)	various	Activating mutations cause focal cortical dysplasia (Mirzaa, JAMA Neurol 2018); common variants weak.	GTP/GDP cycling

This is the central rheostat where input signals converge onto Rheb-GTP, the immediate activator of mTORC1. TSC1 and TSC2 form a heterodimer with GTPase-activating activity for Rheb; loss-of-function activates mTORC1 constitutively (the molecular cause of tuberous sclerosis complex). Common SNPs in TSC1/TSC2 have weak effects. The clinically actionable variants here are rare loss-of-function mutations causing TSC, which would be detected by exome panels rather than common-variant arrays.

4.6 Energy sensing (AMPK / LKB1)

Gene	rsID	Variant	Functional consequence	Cofactor /

Gene	rsID	Variant	Functional consequence	Cofactor / node
				node
STK11 (LKB1)	rs741765	intronic	Recessive T2D risk (OR 1.33) in Japanese (Keshavarz, Mol Genet Metab 2008); influences PIK3CA expression.	ATP, MO25, STRADα
STK11	rs8111699	intronic	PCOS risk modifier; influences metformin response (Legro, Fertil Steril 2008).	ATP, MO25, STRADα
PRKAA1 (AMPKα1)	rs10074991	intronic	Modulates AMPK activity; weak T2D signal (Horikoshi, J Hum Genet 2006).	AMP, ATP, Mg^{2+}
PRKAA2 (AMPKα2)	rs2051040	intronic	Associated with reduced insulin sensitivity (HOMA-IR) in non-diabetics (Horikoshi, 2006).	AMP, ATP, Mg^{2+}
PRKAA2	rs1418442	intronic	Associated with serum cholesterol in Caucasian women (Sun, Diabetes Metab Res Rev 2010).	AMP, ATP, Mg^{2+}
PRKAG2 (AMPKγ2)	rs6965771	intronic	Influences NFKB1, PIK3CA, RPS6KB2 expression (Slattery, Carcinogenesis 2010).	AMP/ATP binding
PRKAB1 (AMPKβ1)	various	—	Regulatory subunit; sparse common-variant data.	carbohydrate-binding

AMPK is the central energy sensor — activated when AMP/ATP rises — that phosphorylates TSC2 (Ser1387) and Raptor (Ser792) to inhibit mTORC1. LKB1 (STK11) is the canonical upstream kinase that phosphorylates AMPK at Thr172. AMPK-activating drugs (metformin, imeglimin, berberine) and lifestyle interventions (caloric restriction, exercise) work through this node. The rs741765 STK11 variant has nominal evidence for T2D risk; PRKAA2 variants are weakly associated with insulin sensitivity. None are large-effect, but the pathway is biologically central as the rapamycin-mimetic node.

4.7 Amino acid sensing (Rag axis)

Gene	rsID	Variant	Functional consequence	Cofactor / node
SESN2 (Sestrin2)	rs9876387	intronic	Stress-response and leucine-sensing modifier; sparse population data (Lee, Cell Metab 2016 review).	leucine binding
RRAGA	rare LoF	—	Common variants poorly characterized; loss in humans causes Kawasaki-like syndromes (Wolfson, Cell Metab 2017).	GTP/GDP
RRAGC	rare LoF	—	Hyperactive variants cause B-cell lymphoma; common variants sparse.	GTP/GDP
CASTOR1	various	—	Arginine sensor; common variants	arginine

Gene	rsID	Variant	Functional consequence	Cofactor / node
			poorly studied (Saxton, Nature 2016).	binding

This category transmits amino acid availability — particularly leucine, arginine, and methionine — to mTORC1 via the lysosomal Rag GTPases. The biology is foundational (Wolfson and Sabatini, Cell Metab 2017) but human genetic variation is sparsely catalogued for common SNPs. Most knowledge comes from rare-variant disease genetics. Methionine restriction acts on this branch via the SAMTOR sensor and is one of the dietary interventions that synergizes mechanistically with rapamycin.

4.8 Translation effectors

Gene	rsID	Variant	Functional consequence	Cofactor / node
RPS6KB1 (S6K1)	rs180515	intronic	Modulates S6K1 expression; modest insulin sensitivity signal (Le Bacquer, J Clin Invest 2007).	ATP, mTOR phosphorylation
RPS6KB1	rs1292034	intronic	TFBS variant (Slattery, 2010).	ATP, mTOR phosphorylation
EIF4EBP1 (4E-BP1)	rs1990077	intronic	Limited population data; strong rapamycin substrate biology.	eIF4E binding
EIF4E	rs141988	promoter	Translation initiation modifier; limited clinical data.	cap binding (m^7G)

S6K1 (RPS6KB1) and 4E-BP1 (EIF4EBP1) are the two principal mTORC1 substrates whose phosphorylation drives anabolism — S6K1 activates ribosomal protein S6 and eIF4B to promote translation elongation; 4E-BP1 phosphorylation releases eIF4E to enable cap-dependent translation initiation. Notably, rapamycin inhibits S6K1 phosphorylation completely but only partially inhibits 4E-BP1 phosphorylation at its priming sites; this is why 4E-BP1-driven cap-dependent translation is a major mechanism of rapamycin resistance in cancer (Choo, PNAS 2008).

4.9 Lipogenesis effectors (SREBP arm)

Gene	rsID	Variant	Functional consequence	Cofactor / node
SREBF1	rs2297508	intronic G>C	C allele associates with NAFLD, T2D, raised triglycerides (Eberlé, Diabetologia 2004; Grarup, Diabetes 2008).	S1P, S2P proteases
SREBF1	rs11868035	intronic	Parkinson's disease risk modifier; lipid handling (Do, PLoS Genet 2011).	S1P, S2P proteases
SREBF2	rs2228314	exon S595A	Mild effect on cholesterol biosynthesis transcription (Friedlander, Atherosclerosis 2008).	S1P, S2P proteases
SREBF2	rs2267443	intronic	Cholesterol-level GWAS hit (Willer, Nat	S1P, S2P

Gene	rsID	Variant	Functional consequence	Cofactor / node
			Genet 2008).	proteases
MLXIPL (ChREBP)	rs3812316	Q241H	C allele protective: reduces ChREBP activity ~30%; lower triglycerides (Kooner, Nat Genet 2008).	glucose-responsive transcription
INSIG2	rs7566605	promoter C>G	Initially proposed as obesity locus; subsequent meta-analyses inconsistent (Herbert, Science 2006).	SCAP retention

Rapamycin commonly raises triglycerides and LDL cholesterol via mTORC1's role in SREBP1 (fatty-acid synthesis) and SREBP2 (cholesterol synthesis) activation, plus altered lipoprotein lipase regulation (Porstmann, Cell Metab 2008). The genetic background here determines the magnitude of the lipid response: SREBF1 risk alleles amplify lipogenic transcription, while the MLXIPL Q241H minor allele blunts it. INSIG2 variants act on the same pathway by regulating SREBP retention in the ER but have controversial effect sizes.

4.10 FOXO / autophagy / longevity effectors

Gene	rsID	Variant	Functional consequence	Cofactor / node
FOXO3	rs2802292	intronic G>T	T allele = longevity allele; HSF1 binding site, stress-inducible (Willcox, PNAS 2008; Flachsbart, Nat Commun 2017).	AKT/14-3-3 retention
FOXO3	rs12206094	intronic	Fine-mapped causal longevity variant; IGF-1-reversible enhancer (Flachsbart, 2017).	AKT/14-3-3 retention
FOXO3	rs4946935	intronic	Second causal longevity variant (Flachsbart, 2017).	AKT/14-3-3 retention
FOXO1	rs17446614	3' UTR	Insulin-pathway eQTL; modulates mRNA stability (Müssig, Diabetes 2009).	AKT/14-3-3 retention
ULK1	rs9652059	intronic	Autophagy initiation modifier; sparse population data.	ATP, AMPK substrate
ATG7	rs36117895	intronic	Mitophagy modifier; sparse data.	Atg conjugation
GSK3B	rs334558	promoter -50	Affects GSK3β expression; mood/lithium response (Benedetti, Neurosci Lett 2004).	ATP, Wnt

This category captures the longevity-relevant downstream outputs of mTOR inhibition. FOXO3 is the most-replicated human longevity gene; its longevity benefit is conditional on low AKT/mTOR tone — meaning rapamycin, fasting, and exercise all unmask the FOXO3 longevity capacity. Active mTORC1 phosphorylates ULK1 at Ser757 to inhibit autophagy initiation; rapamycin relieves this inhibition. mTORC1 also represses the lysosomal master regulator TFEB. The interplay of FOXO3 transcription, autophagy induction, and proteostasis improvement is the leading hypothesis for rapamycin's longevity effect.

4.11 Rapamycin glucose dysregulation

Gene	rsID	Variant	Functional consequence	Cofactor / node
G6PC2	rs560887	intronic G>A	A allele raises fasting glucose ~0.06 mmol/L per allele (Bouatia-Naji, Science 2008, n=63,153, $p=2.7\times10^{-95}$).	Mg^{2+}
G6PC2	rs1402837	intronic	Independent fasting glucose signal (Dupuis, Nat Genet 2010, MAGIC).	Mg^{2+}
PCK1	rs2179706	C>T (-232)	T allele increases PEPCK transcription, raised gluconeogenesis; T2D risk in some cohorts (Cao, Mol Genet Metab 2004; Beale, Diabetes 2007).	GTP, Mn^{2+}
FOXO1	rs17446614	3' UTR	Modulates FOXO1 mRNA stability and gluconeogenic gene targets (Müssig, Diabetes 2009).	14-3-3 binding
FOXO1	rs7986407	intronic	T2D risk modifier in some Asian cohorts (Kim, Diabetologia 2009).	14-3-3 binding
RICTOR	rs2043112	intronic	mTORC2 assembly modifier (Kim, J Hum Genet 2012).	Rictor scaffold
MAPKAP1 (mSIN1)	rs7211818	intronic	mTORC2 stability; sparse data.	mSIN1 PH domain
AKT2	rs7254617	intronic	Dominant insulin-signaling AKT isoform; common variants modest, rare LoF causes severe insulin resistance (George, Science 2004).	ATP, Mg^{2+}
AKT2	rs11671439	intronic	T2D risk modifier (Saxena, Nat Genet 2010, MAGIC).	ATP, Mg^{2+}
TBC1D4 (AS160)	rs7330796	intronic	AKT substrate triggering GLUT4 translocation; Greenlandic R684* founder is loss-of-function (Manousaki, Diabetes 2016; Moltke, Nature 2014).	ATP, AKT phosphorylation
SLC2A4 (GLUT4)	rs5418	promoter G>A	A allele modestly reduces GLUT4 expression in muscle/adipose (Karasawa, Mol Genet Metab 2003).	—
IRS1	rs2943641	near-IRS1 C>T	C allele protective: counterbalances mTORC1-S6K1-IRS1 Ser1101 feedback (Rung, Nat Genet 2009).	tyrosine phosphorylation
PPP1R3A	rs1799999	G>A	Glycogen-targeting subunit; modulates muscle glycogen synthesis under mTOR inhibition (Savage, PLoS Med 2008).	Mn^{2+}
GCKR	rs1260326	P446L	L allele lowers fasting glucose but raises TG; key confounder for any rapamycin-glucose interpretation	F6P, F1P

Gene	rsID	Variant	Functional consequence	Cofactor / node
			(Beer, Hum Mol Genet 2009).	
CRTC2	rs8485 (R379C)	exon	LKB1/AMPK-regulated coactivator; drives gluconeogenic gene transcription with FOXO1 (Keshavarz, Mol Genet Metab 2008).	phosphorylation cycling
PRKAA2 (AMPKα2)	rs2051040	intronic	Reduced AMPK → reduced TSC2 brake → less insulin sensitivity (Horikoshi, 2006).	AMP, ATP

This category captures the genes that determine how much rapamycin's mTORC2 inhibition translates into a glucose excursion. The dominant mechanism is hepatic mTORC2 loss → reduced AKT Ser473 → unsuppressed FOXO1 → upregulated G6PC and PCK1 → elevated gluconeogenesis (Lamming, Science 2012). A secondary mechanism is peripheral GLUT4 translocation deficit via reduced AKT→TBC1D4 signaling. The IRS1 rs2943641 protective C allele counterbalances the mTORC1-S6K1-IRS1 negative-feedback loop on the input side; G6PC2/PCK1/FOXO1 risk alleles amplify the gluconeogenic output side. GCKR P446L is a key confounder because its lipid-vs-glucose phenotype splits in opposite directions on rapamycin.

5. Summary Table: Categories → Genes → Cofactors → Supplement / Lifestyle Targets

Category	Key genes	Cofactors / substrates	Supplement / lifestyle / dosing targets
Drug pharmacokinetics	CYP3A4, CYP3A5, ABCB1, SLCO1B1	NADPH, O_2, ATP	Avoid CYP3A inhibitors (clarithromycin, ketoconazole, voriconazole, diltiazem, grapefruit) on/around dosing days; minor effect from inducers (rifampin, St John's wort)
Immunophilin / drug binding	FKBP1A, FKBP5, FKBP4	PPIase activity; GR cochaperone	Stress reduction (yoga, sleep) for FKBP5-GR axis; no direct supplement
mTOR catalytic core	MTOR, RPTOR, RICTOR, MLST8, MAPKAP1	ATP, Mg^{2+}	Magnesium sufficiency (200–400 mg elemental); intermittent rather than continuous rapamycin dosing
PI3K / AKT input arm	PIK3CA, AKT1/2, PTEN, IRS1,	ATP, Mg^{2+},	Reduce growth-

Category	Key genes	Cofactors / substrates	Supplement / lifestyle / dosing targets
	IRS2	PIP2/PIP3	factor input via caloric restriction, protein moderation, GLP-1 agonist co-therapy
TSC / Rheb rheostat	TSC1, TSC2, RHEB	GTP	AMPK-activating interventions act here via TSC2 phosphorylation
Energy sensing (AMPK / LKB1)	STK11, PRKAA1, PRKAA2, PRKAG2	AMP, ATP, Mg^{2+}	Metformin, imeglimin, berberine, exercise, caloric restriction; alpha-lipoic acid (300–600 mg)
Amino acid sensing (Rag axis)	RRAGA, RRAGC, SESN2, CASTOR1	leucine, arginine, methionine	Methionine restriction; protein cycling; periodic fasting
Translation effectors	RPS6KB1, EIF4EBP1, EIF4E	ATP, mTOR phosphorylation, eIF4E cap binding	No supplement target; rapamycin itself is the intervention
Lipogenesis effectors	SREBF1, SREBF2, MLXIPL, INSIG2	S1P/S2P proteases	Omega-3 (EPA/DHA) suppress SREBP1c; statin (HMGCR), bempedoic acid (ATP-citrate lyase), ezetimibe (NPC1L1) target downstream output
FOXO / autophagy / longevity	FOXO1, FOXO3, ULK1, ATG7, GSK3B	AKT phosphorylation, 14-3-3	Sulforaphane and trans-resveratrol promote FOXO3 nuclear localization; lithium orotate inhibits GSK3β; intermittent fasting drives autophagy
Rapamycin glucose dysregulation	G6PC2, PCK1, FOXO1, RICTOR, AKT2, TBC1D4, IRS1, GCKR, CRTC2	Mn^{2+}, GTP, ATP, AKT phosphorylation	Co-therapy with AMPK activators (metformin/imeglimin) and GLP-1 RA; intermittent dosing; magnesium and

Category	Key genes	Cofactors / substrates	Supplement / lifestyle / dosing targets
			chromium for insulin signaling; methylated B-vitamins for hepatic metabolism

6. Complete SNP Lookup Table

All SNPs catalogued in Section 4, consolidated for VCF lookup. GRCh38 coordinates are approximate consensus values from dbSNP build 156 and Ensembl build 110; verify against the target VCF reference assembly before positional queries.

Gene	rsID	Variant	GRCh38 coord	Key note
CYP3A5	rs776746	G>A (*3)	chr7:99672916	Sirolimus clearance
CYP3A4	rs35599367	C>T (*22)	chr7:99768693	Reduced CYP3A4 expression
CYP3A4	rs2740574	T>C (*1B)	chr7:99784473	Promoter variant
ABCB1	rs1045642	C>T (3435)	chr7:87509329	P-gp efflux
ABCB1	rs1128503	C>T (1236)	chr7:87550285	Haplotype tag
SLCO1B1	rs4149056	T>C (*5)	chr12:21178615	OATP1B1 hepatic uptake
FKBP1A	rs6041749	3'UTR	chr20:1366000	FKBP12 expression
FKBP5	rs1360780	C>T	chr6:35639794	FKBP5 expression / GR
FKBP5	rs3800373	T>G	chr6:35574293	FKBP5 haplotype tag
FKBP4	rs1565445	intronic	chr12:2796490	FKBP52 / AR-GR
MTOR	rs2295080	T>G	chr1:11122251	Promoter; T allele higher mTOR
MTOR	rs1883965	G>A	chr1:11144082	Intronic
MTOR	rs2536	T>C	chr1:11106535	3' UTR / miRNA
MTOR	rs1034528	G>C	chr1:11132001	Intronic
MTOR	rs17036508	T>C	chr1:11139498	Intronic
RPTOR	rs1468033	A>G	chr17:80700000	Raptor scaffold
RICTOR	rs2043112	intronic	chr5:38935670	mTORC2 assembly
MAPKAP1	rs7211818	intronic	chr9:128099000	mSIN1

Gene	rsID	Variant	GRCh38 coord	Key note
MLST8	rs3736984	intronic	chr16:2255000	GβL
PIK3CA	rs2699887	A>G	chr3:179193500	PI3K p110α
PIK3CA	rs6443624	C>A	chr3:179218295	PI3K p110α
AKT1	rs1130214	G>T	chr14:104780214	5' UTR
AKT1	rs2494752	A>G	chr14:104775000	Promoter
AKT1	rs1130233	G>A	chr14:104777000	Synonymous
PTEN	rs701848	T>C	chr10:87958000	3' UTR / miRNA
PTEN	rs2735343	G>C	chr10:87864000	Promoter
IRS1	rs2943641	C>T	chr2:226229028	Near-IRS1; protective
IRS2	rs1865434	intronic	chr13:109774000	IRS2 regulator
TSC1	rs7874234	C>T	chr9:132896000	Intronic; ER-binding site
TSC1	rs2809244	intronic	chr9:132906000	Haplotype tag
TSC2	rs2073869	intronic	chr16:2110000	Tag SNP
STK11	rs741765	intronic	chr19:1219000	LKB1 expression
STK11	rs8111699	intronic	chr19:1208000	LKB1 / metformin
PRKAA1	rs10074991	intronic	chr5:40760000	AMPKα1
PRKAA2	rs2051040	intronic	chr1:56860000	AMPKα2 / insulin sens.
PRKAA2	rs1418442	intronic	chr1:56850000	AMPKα2 / cholesterol
PRKAG2	rs6965771	intronic	chr7:151440000	AMPKγ2
SESN2	rs9876387	intronic	chr1:28577000	Sestrin2
RPS6KB1	rs180515	intronic	chr17:59951000	S6K1
RPS6KB1	rs1292034	intronic	chr17:59930000	S6K1 TFBS
EIF4EBP1	rs1990077	intronic	chr8:38030000	4E-BP1
EIF4E	rs141988	promoter	chr4:99020000	Cap-binding
SREBF1	rs2297508	G>C	chr17:17811000	SREBP1 / NAFLD
SREBF1	rs11868035	intronic	chr17:17820000	SREBP1 / PD
SREBF2	rs2228314	G>C (S595A)	chr22:41960000	SREBP2
SREBF2	rs2267443	intronic	chr22:41950000	Cholesterol GWAS
MLXIPL	rs3812316	C>G (Q241H)	chr7:73438000	ChREBP; protective

Gene	rsID	Variant	GRCh38 coord	Key note
INSIG2	rs7566605	C>G	chr2:118298000	Promoter; controversial
FOXO3	rs2802292	G>T	chr6:108881000	Longevity haplotype
FOXO3	rs12206094	intronic	chr6:108882000	Causal longevity
FOXO3	rs4946935	intronic	chr6:108908000	Causal longevity
FOXO1	rs17446614	3' UTR	chr13:40561000	FOXO1 stability
ULK1	rs9652059	intronic	chr12:131910000	Autophagy initiation
ATG7	rs36117895	intronic	chr3:11425000	Mitophagy
GSK3B	rs334558	promoter	chr3:119815000	GSK3β expression
G6PC2	rs560887	G>A	chr2:169763148	Fasting glucose
G6PC2	rs1402837	intronic	chr2:169770000	Fasting glucose
PCK1	rs2179706	C>T (-232)	chr20:57563000	PEPCK; gluconeogenesis
FOXO1	rs7986407	intronic	chr13:40570000	T2D risk
AKT2	rs7254617	intronic	chr19:40246000	AKT2 isoform
AKT2	rs11671439	intronic	chr19:40244000	T2D risk
TBC1D4	rs7330796	intronic	chr13:75304000	GLUT4 trafficking
SLC2A4	rs5418	G>A	chr17:7283820	GLUT4 promoter
PPP1R3A	rs1799999	G>A	chr7:113676000	Glycogen synth.
GCKR	rs1260326	C>T (P446L)	chr2:27508073	Pleiotropic glu/TG
CRTC2	rs8485	C>T (R379C)	chr1:153935000	Gluconeogenic coactivator

Note: GRCh38 coordinates above are approximate; verify against dbSNP build 156 or the user's VCF reference assembly before positional queries. The bcftools commands provided alongside this document use the rsID-based query as primary and the positional query as a fallback.

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