Glucose Regulation

Genetic Pathway Reference

14 Functional Categories • ~85 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of glucose homeostasis, the genes that govern each node of insulin secretion and action, the well-studied common variants in those genes, the cofactors each enzyme or signaling component depends on, and the supplement and dietary targets that map to each cofactor and pathway. It is intended for use by clinicians, researchers, 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 and peer-reviewed mechanistic studies. 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 (odds ratios 1.1–1.4 per allele); clinical significance arises from cumulative patterns and gene-environment interactions. A small number of variants — notably TCF7L2 rs7903146, MTNR1B rs10830963, KCNJ11 E23K, CDKAL1 rs7756992, FTO rs9939609, PPARG Pro12Ala, the TBC1D4 Greenlandic founder variant, and the LADA-defining HLA-DQB1, PTPN22 R620W, and INS VNTR variants — have larger and clinically actionable effect sizes.

2. Pathway Biology

2.1 What glucose homeostasis is

Glucose homeostasis is the minute-to-minute stabilization of plasma glucose within approximately 70–140 mg/dL despite episodic intake and continuous utilization. It is the canonical example of a physiological control system with sensors (pancreatic beta- and alpha-cells, hepatic and hypothalamic glucose sensors), effectors (insulin, glucagon, incretins GLP-1 and GIP, catecholamines, cortisol), and target tissues (liver, skeletal muscle, adipose tissue, brain, kidney). Failure at any node produces the continuum from impaired fasting glucose to impaired glucose tolerance to type 2 diabetes to beta-cell failure (DeFronzo, Diabetes 2009; Ashcroft & Rorsman, Cell 2012).

Type 2 diabetes is not one disease. Genome-wide association studies of more than one million individuals now identify approximately 500 independent T2D loci, and cluster analyses partition them into at least five pathophysiological processes: beta-cell dysfunction with proinsulin deficiency, beta-cell dysfunction with intact proinsulin, obesity-driven insulin resistance, lipodystrophy-like insulin resistance, and hepatic/lipid metabolism (Udler et al., PLoS Med 2018; Mahajan et al., Nat Genet 2022). This partitioning matters because the genetic architecture of a given individual indicates which node is breaking.

2.2 The beta cell as the central actor

Most T2D GWAS signal — and the strongest effect sizes — map to beta-cell biology rather than insulin resistance. The canonical beta-cell stimulus-secretion coupling sequence is: glucose

enters via GLUT2 (SLC2A2) and, in humans, GLUT1 (SLC2A1); glucokinase (GCK) phosphorylates it, establishing the glucose sensor with sigmoidal kinetics that set the secretion threshold around 5 mM; glycolysis and mitochondrial oxidation raise the ATP/ADP ratio; rising ATP/ADP closes the KATP channel (Kir6.2 encoded by KCNJ11, SUR1 encoded by ABCC8); membrane depolarization opens voltage-gated calcium channels (CACNA1D, CACNA1C); calcium influx triggers fusion of insulin granules, whose content includes insulin, C-peptide, amylin, and zinc ions (zinc transporter SLC30A8/ZnT8 crystallizes insulin hexamers). First-phase release (approximately 5 min) is from docked granules; second-phase requires granule recruitment and mitochondrial amplification (Henquin, Diabetologia 2009).

Proinsulin is processed to insulin and C-peptide by prohormone convertases (PCSK1, PCSK2) and carboxypeptidase E. tRNA-modification enzymes like CDKAL1 are required for accurate translation of proinsulin; CDKAL1 loss causes mistranslation and endoplasmic reticulum stress (Wei et al., J Clin Invest 2011).

2.3 Incretins — the gut axis

Oral glucose produces approximately twice the insulin response of matched IV glucose. This incretin effect is mediated by GLP-1 (from intestinal L-cells, encoded at GCG) and GIP (from K-cells). Both bind Gs-coupled receptors (GLP1R, GIPR) on beta cells, raising cAMP and amplifying glucose-stimulated insulin secretion. GLP-1 also suppresses glucagon and slows gastric emptying. The incretin effect is markedly reduced in T2D, partly because of beta-cell receptor desensitization but also because of genetic variation at TCF7L2 — the strongest common-variant signal in T2D — which impairs GLP-1 action on the beta cell (Lyssenko et al., J Clin Invest 2007). Pharmacological GLP-1 and dual GLP-1/GIP agonists bypass this defect by directly activating receptors.

2.4 Insulin signaling and peripheral disposal

Insulin binds the insulin receptor (INSR), activating tyrosine kinase activity that phosphorylates IRS1 and IRS2. IRS1 recruits PI3K, generating PIP3 and activating AKT. AKT has three key outputs relevant to glucose: translocation of GLUT4 (SLC2A4) to the plasma membrane in muscle and fat; glycogen synthesis via GSK3-beta inhibition; and nuclear export of FOXO1, shutting off hepatic gluconeogenic genes including PCK1 and G6PC. Insulin resistance is defined biochemically at the IRS1 → PI3K → AKT node; compensatory hyperinsulinemia maintains glucose until beta cells fail (Petersen & Shulman, Physiol Rev 2018).

2.5 Hepatic glucose output and the glucokinase regulatory system

The liver both stores glucose postprandially and produces it during fasting via gluconeogenesis. Key regulators are GCK (hepatic isoform, with a different promoter than the beta-cell isoform), GCKR (glucokinase regulatory protein, which sequesters GCK in the nucleus when fructose-6-phosphate is high), G6PC (glucose-6-phosphatase, the terminal gluconeogenic enzyme), PCK1 (PEPCK), and FOXO1. The GCKR P446L variant (rs1260326) is one of the most pleiotropic metabolic variants ever described, simultaneously lowering fasting glucose while raising triglycerides and uric acid (Orho-Melander et al., Diabetes 2008; Vaxillaire et al., Diabetes 2008; Saxena et al., Science 2007).

2.6 Adipose tissue as an endocrine organ

Adipose is not a passive fat depot. Adipocytes secrete adiponectin (insulin-sensitizing, anti-inflammatory), leptin (satiety, insulin sensitization), resistin, and inflammatory cytokines. Low adiponectin precedes T2D onset. PPARG is the master transcription factor of adipogenesis and

the pharmacological target of thiazolidinediones. The PPARG Pro12Ala variant (rs1801282) was one of the first T2D variants ever identified (Altshuler et al., Nat Genet 2000). FTO, the strongest GWAS signal for BMI, acts in part via distal IRX3/IRX5 in adipocyte progenitors, shifting white versus beige fat fate (Claussnitzer et al., NEJM 2015).

2.7 Circadian regulation

Beta cells express a functional circadian clock (BMAL1, CLOCK, PER, CRY); beta-cell Bmal1 knockout in mice produces glucose intolerance (Marcheva et al., Nature 2010). MTNR1B (melatonin receptor 1B) is expressed on beta cells and mediates melatonin's inhibition of insulin secretion. The rs10830963 G allele raises fasting glucose and T2D risk by approximately 9 percent per allele by increasing MTNR1B expression — one of the largest fasting glucose GWAS signals (Prokopenko et al., Nat Genet 2009; Lyssenko et al., Nat Genet 2009; Tuomi et al., Cell Metab 2016). This makes nocturnal eating and high-dose evening melatonin supplementation particularly relevant considerations for carriers.

2.8 Vitamin D and the beta cell

Beta cells express the vitamin D receptor (VDR); 1,25-dihydroxyvitamin D upregulates insulin gene transcription and supports beta-cell survival. Observational data consistently link low 25(OH)D to T2D risk. The D2d randomized trial tested 4000 IU/day vitamin D3 in prediabetes; the primary endpoint was negative but per-protocol and subgroup analyses suggested benefit in vitamin D-insufficient participants (Pittas et al., NEJM 2019). CYP2R1 is the rate-limiting 25-hydroxylase; GC is the vitamin D binding protein; VDR determines downstream signal transduction.

2.9 Cofactors across the pathway

Glucose homeostasis depends on a recurring set of micronutrient and metabolic cofactors: zinc (insulin hexamer crystallization via ZnT8, insulin receptor function); magnesium (ATP/ADP generation, insulin receptor tyrosine kinase, glucokinase activity; hypomagnesemia predicts incident T2D per Barbagallo & Dominguez, Arch Biochem Biophys 2007); chromium (modest insulin signaling enhancement via chromodulin model); vitamin D 1,25-dihydroxy form (insulin gene transcription, beta-cell survival); biotin (cofactor for pyruvate carboxylase in gluconeogenesis and anaplerosis); NAD+/NADH (glyceraldehyde-3-phosphate dehydrogenase, mitochondrial electron transport); manganese (SOD2 cofactor for beta-cell mitochondrial antioxidant defense); selenium (GPX1/GPX4 downstream of SOD2, though excess selenium paradoxically impairs insulin sensitivity per Stranges et al., Ann Intern Med 2007); and the methyl donors folate, B12, and betaine (insulin gene promoter methylation and beta-cell epigenetics).

2.10 Clinical integration

The five physiological subtypes of T2D (Udler et al., PLoS Med 2018) are clinically useful: beta-cell dysfunction with proinsulin deficiency; beta-cell dysfunction with intact proinsulin; obesity-mediated insulin resistance; lipodystrophy-like insulin resistance; and liver/lipid metabolism. A polygenic pattern dominated by beta-cell variants (KCNJ11, ABCC8, CDKAL1, TCF7L2, GCK, MTNR1B, HHEX) with intact insulin-signaling genes (IRS1, PPARG, FTO) indicates a secretion-limited phenotype — responsive to beta-cell-supporting agents (imeglimin, incretin mimetics, insulin) and insulin-independent glucose lowering (SGLT2 inhibitors, acarbose) rather than primarily insulin sensitizers. The opposite pattern — strong FTO/PPARG/IRS1 risk with clean

beta-cell loci — suggests a resistance-dominant phenotype better served by weight loss, metformin, and TZDs.

2.11 Latent autoimmune diabetes in adults (LADA)

LADA is an adult-onset form of autoimmune diabetes characterized by the presence of islet autoantibodies (most commonly anti-GAD65) at diagnosis but with preserved beta-cell function sufficient to delay insulin requirement for at least six months. It is sometimes referred to as type 1.5 diabetes. Epidemiologically it is the most common form of adult-onset autoimmune diabetes, representing approximately 4–12 percent of patients diagnosed clinically with T2D depending on the population (Tuomi et al., Lancet 2014; Buzzetti et al., Diabetes 2020 consensus statement).

LADA has a hybrid genetic architecture. The first genome-wide association study of LADA (Cousminer et al., Diabetes Care 2018; n = 2,634 cases vs 5,947 controls) found four loci reaching genome-wide significance, all of them established T1D risk loci: HLA class II, PTPN22, INS, and SH2B3. The HLA-DQB1 lead SNP rs9273368 had OR ≈ 3.30 (95% CI 2.81–3.88, $p = 1.89\times10^{-47}$) in the highest GADA-titer tertile and OR ≈ 2.42 in the lowest tertile — the strongest single signal in adult diabetes genetics. Importantly, in the same study TCF7L2 rs7903146 (the T2D signature variant) was also associated with LADA, with the effect being slightly stronger in the low-GADA-titer subgroup, demonstrating the T2D-LADA overlap in patients with milder autoimmunity. A novel LADA-specific signal at PFKFB3 was also identified, mechanistically interesting because PFKFB3 sits at the intersection of insulin signaling, glycolysis regulation, and inflammatory signaling (Mishra et al., BMC Med 2017; Cousminer et al., Diabetes Care 2018).

The clinical importance of recognizing a LADA-compatible genetic profile is therapeutic. LADA patients progress to insulin dependence faster than typical T2D patients, often within 6 years of diagnosis (UKPDS, Turner et al., Lancet 1997). Early identification supports anti-GAD antibody testing, consideration of beta-cell preservation strategies, avoidance of sulfonylurea-driven beta-cell exhaustion, and earlier integration of insulin-sparing approaches (DPP-4 inhibitors, GLP-1 agonists, and in some studies low-dose insulin to preserve residual beta-cell function). PTPN22 R620W is also a major signal in the inflammation and immune pathway (rheumatoid arthritis, SLE, type 1 diabetes), and its presence here bridges the metabolic and autoimmune pathway documents.

3. Functional Categories

The glucose regulation pathway can be organized into fourteen functional categories, each corresponding to a distinct biochemical, cellular, or immunological job. The categories below are used as the organizing scaffold for the SNP catalog in Section 4.

#	Category	Function	Key genes
1	Beta-cell transcription factors	Beta-cell identity, Wnt signaling, melatonin-clock coupling	TCF7L2, HHEX, PROX1, HNF1A, HNF1B, HNF4A, PDX1, MTNR1B
2	Glucose sensing (glucokinase axis)	Set the glucose threshold for secretion and hepatic output	GCK, GCKR, G6PC2, ADCY5, DGKB, MADD, SLC2A2
3	KATP channel & exocytosis	Electrical trigger of insulin release, granule exocytosis	KCNJ11, ABCC8, KCNQ1, CACNA1D, CACNA1E, SLC30A8

#	Category	Function	Key genes
4	Proinsulin processing & ER	Insulin translation, folding, maturation, ER stress handling	CDKAL1, INS, IGF2BP2, WFS1
5	Incretin axis	Gut-derived amplification of insulin secretion	GLP1R, GIPR, DPP4, GCG (TCF7L2 overlap)
6	Insulin signaling & peripheral sensitivity	INSR → IRS1 → PI3K → AKT → GLUT4 cascade	INSR, IRS1, PIK3R1, AKT2, SLC2A4, TBC1D4
7	Hepatic glucose output	Gluconeogenesis and hepatic glucose production	GCKR, G6PC2, PCK1, FOXO1, PPP1R3B, CREB3L2
8	Adiposity, adipokines & lipid crosstalk	Obesity-driven resistance, adipose endocrine function	PPARG, FTO, MC4R, ADIPOQ, LEP, LEPR, IRS2, LPIN1
9	Circadian / meal-timing	Clock regulation of insulin secretion and glucose tolerance	MTNR1B, CRY2, PER2, CLOCK, ARNTL (BMAL1)
10	Vitamin D–glucose axis	25(OH)D production, transport, and receptor signaling	CYP2R1, GC, VDR
11	Mitochondrial function & oxidative stress	Beta-cell oxidative defense; glucotoxicity resistance	SOD2, GPX1, UCP2, NDUFB6
12	Inflammation & metabolic stress	Sub-clinical inflammation impairing insulin signaling	IL6, TNF, CRP, IL1B, IL10
13	Pharmacogenomics of antidiabetic drugs	Drug transport, metabolism, and response	SLC22A1 (OCT1), SLC47A1 (MATE1), ATM, CYP2C9, GLP1R, KCNJ11/ABCC8
14	Latent autoimmune diabetes (LADA)	Autoimmune-flavored adult diabetes (T1D / T2D hybrid)	HLA-DQB1, HLA-DQA1, PTPN22, INS, SH2B3, PFKFB3, CTLA4, IL2RA, BACH2, IFIH1

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(s) or pathway node required by the associated protein. Effect sizes and GWAS p-values are noted where well established. The largest-effect and most clinically actionable variants are flagged in the interpretive paragraph below each table.

4.1 Beta-cell transcription factors

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
TCF7L2	rs7903146	intronic C>T	Strongest common T2D signal; T allele impairs beta-cell function, proinsulin conversion, and GLP-1 action; OR ≈ 1.37–1.46 per allele, $p < 10^{-48}$ (Grant, Nat Genet 2006)	Wnt/beta-catenin; GLP-1 signaling
TCF7L2	rs12255372	intronic G>T	In LD with rs7903146; reinforces beta-cell dysfunction signal	Wnt/beta-catenin
HHEX	rs1111875	near-gene T>C	Reduced beta-cell development; OR ≈ 1.13 (Sladek, Nature 2007)	Homeobox transcription
HHEX	rs7923837	near-gene A>G	Second HHEX signal; modest developmental effect on beta-cell mass	Homeobox transcription
PROX1	rs340874	promoter C>T	Fasting glucose association; beta-cell development and hepatic metabolism (Dupuis, MAGIC 2010)	Transcription factor; Wnt crosstalk
HNF1A	rs1169288	I27L missense	Modest T2D risk; rare coding variants cause MODY3	Nuclear cofactors; rare MODY3 gene
HNF1B	rs4430796	intronic A>G	T2D and prostate cancer pleiotropy (Gudmundsson, Nat Genet 2007)	Nuclear cofactors; rare MODY5 gene
HNF4A	rs4812829	intronic	Fasting glucose and T2D signal in some populations	Nuclear cofactors; rare MODY1 gene
MTNR1B	rs10830963	intronic C>G	G allele raises MTNR1B expression, inhibits nocturnal insulin secretion; fasting glucose +0.07 mmol/L/allele, T2D OR ≈ 1.09, $p < 10^{-29}$ (Prokopenko, Nat Genet 2009; Lyssenko, Nat Genet 2009)	Melatonin signaling; circadian
MTNR1B	rs1387153	near-gene	Secondary fasting glucose signal at the MTNR1B locus	Melatonin signaling

The largest effects in this category are TCF7L2 rs7903146 and MTNR1B rs10830963. TCF7L2 is the single strongest common-variant T2D signal; its risk allele simultaneously impairs intrinsic beta-cell function, proinsulin processing, and responsiveness to GLP-1. Pharmacological GLP-1/GIP agonists bypass the receptor-level defect by directly activating the downstream receptor. MTNR1B rs10830963 illustrates why nocturnal melatonin exposure — from supplementation or late light — is metabolically consequential for carriers, since the G allele sensitizes beta cells to melatonin's inhibitory effect.

4.2 Glucose sensing and the glucokinase axis

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
GCK	rs1799884	-30G>A promoter	Raises fasting glucose by ~0.06 mmol/L per allele, $p < 10^{-25}$ (Weedon, AJHG 2006; MAGIC). Elevates beta-cell glucose sensing threshold	Mg^{2+}, ATP; glucose kinase
GCK	rs4607517	near-gene	Second fasting glucose signal at the GCK locus	Mg^{2+}, ATP
GCKR	rs1260326	P446L C>T	T allele reduces GCKR sequestration of hepatic GCK, lowering fasting glucose but raising triglycerides and uric acid — highly pleiotropic (Orho-Melander, Diabetes 2008)	Fructose-6-P sensing; regulatory protein
G6PC2	rs560887	intronic	Largest per-allele fasting glucose effect, ~0.075 mmol/L (Bouatia-Naji, Science 2008)	Glucose-6-phosphatase (beta-cell)
ADCY5	rs11708067	intronic A>G	Fasting glucose and incretin-stimulated insulin secretion (Dupuis, Nat Genet 2010)	cAMP signaling; adenylyl cyclase
DGKB	rs2191349	intronic	Fasting glucose locus (MAGIC)	DAG kinase; PKC regulation
MADD	rs7944584	intronic	Proinsulin-to-insulin conversion ratio (Strawbridge, Diabetes 2011)	Granule processing
SLC2A2	rs11920090	intronic	Fasting glucose association; GLUT2 beta-cell/hepatic glucose sensor. Rare LOF causes Fanconi-Bickel syndrome	Glucose transporter

This category defines the hepatic and beta-cell glucostat. GCK promoter variation raises the glucose set-point for insulin secretion modestly but durably. GCKR rs1260326 is the clearest metabolic trade-off variant in the human genome: the allele that improves fasting glucose simultaneously worsens the lipid profile, reflecting glucokinase's dual role in glucose phosphorylation and de novo lipogenesis substrate provision. G6PC2 is the largest single fasting-glucose effect discovered by MAGIC.

4.3 KATP channel and exocytosis

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
KCNJ11	rs5219	E23K C>T	K allele reduces ATP sensitivity, impairing channel closure and insulin release; OR ≈ 1.14, $p < 10^{-8}$ (Gloyn, Diabetes 2003)	ATP/ADP sensing; sulfonylurea target
KCNJ11	rs5215	intronic	In LD with E23K; reinforces signal	ATP/ADP sensing
ABCC8	rs757110	S1369A A>C	SUR1 regulatory subunit of KATP; OR ≈ 1.14	ADP/Mg^{2+} sensing; sulfonylurea binding
KCNQ1	rs2237892	intronic	Strongest T2D signal in East Asian	Voltage-gated K+

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
		C>T	populations; OR ≈ 1.29–1.40 (Yasuda/Unoki, Nat Genet 2008). Affects first-phase insulin secretion	channel
KCNQ1	rs231362	intronic	European T2D signal at the KCNQ1 locus	Voltage-gated K+ channel
CACNA 1D	rs312457	intronic	T2D locus; voltage-gated L-type calcium channel subunit	Ca^{2+} influx; depolarization
SLC30A 8	rs13266634	R325W C>T	C allele (Arg) is risk, OR ≈ 1.18 (Sladek, Nature 2007). Rare LOF variants are protective (Flannick, Nat Genet 2014)	Zn^{2+}; insulin hexamer crystallization

This category is the electrical trigger of insulin secretion and the direct target of sulfonylureas. The KCNJ11 E23K / ABCC8 S1369A haplotype is near-universal in T2D GWAS and determines how tightly the KATP channel closes in response to ATP. Paradoxically, SLC30A8 illustrates that common risk variants and rare loss-of-function variants at the same gene can have opposite disease effects — a reminder that GWAS hits do not always tell you the direction a drug should push.

4.4 Proinsulin processing and ER

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
CDKAL1	rs7756992	intronic A>G	Impaired tRNA-Lys methylthio-modification causes proinsulin misreading and ER stress; OR ≈ 1.12–1.20 (Steinthorsdottir, Nat Genet 2007; Wei, JCI 2011)	Fe-S cluster; methylthiotransferase
CDKAL1	rs10946398	intronic A>C	Second CDKAL1 signal; reduced first-phase insulin secretion	Fe-S cluster
IGF2BP2	rs4402960	intronic T>G	OR ≈ 1.14 (Scott, Science 2007); mRNA-binding protein for IGF2 and insulin locus	RNA-binding
WFS1	rs10010131	intronic	OR ≈ 1.11 (Sandhu, Nat Genet 2007); ER calcium homeostasis. Rare LOF causes Wolfram syndrome	ER Ca^{2+}; unfolded protein response
INS/IGF2	rs689	VNTR proxy	Modest T2D effect; stronger T1D association via INS VNTR class	Insulin locus regulation

CDKAL1 is one of the most reproducible beta-cell T2D loci and a mechanistic rarity: it encodes a tRNA-modifying enzyme that uses an Fe-S cluster to methylthiolate lysine codons, and loss of this modification specifically corrupts proinsulin translation, driving ER stress. Because the defect is cumulative over the lifespan of a beta cell, CDKAL1 risk carriers benefit from any intervention that lowers secretory demand (caloric restriction, SGLT2 inhibition, GLP-1 agonism, acarbose).

4.5 Incretin axis

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
GLP1R	rs10305492	A316T missense	Lowers fasting glucose and T2D risk — human genetic validation of GLP-1R agonism (Scott, Diabetes 2016)	Gs/cAMP; GLP-1 signaling
GLP1R	rs6923761	G168S missense	Linked to differential response to GLP-1 receptor agonists in some studies	Gs/cAMP
GIPR	rs10423928	E354Q intronic	Affects insulin response to oral glucose and BMI (Saxena, Nat Genet 2010)	Gs/cAMP; GIP signaling
DPP4	rs6741949	intronic	Modest effect on dipeptidyl peptidase-4 activity and GLP-1 half-life	Serine protease; DPP-4 inhibitor target
TCF7L2	rs7903146 (reprised)	intronic C>T	Dual role: also impairs GLP-1 action on the beta cell	GLP-1 → beta-cell coupling

The GLP1R A316T variant is one of the clearest cases of human genetic validation of a drug class: the same direction of effect (lower glucose, lower T2D risk) is produced both by the protective allele and by GLP-1 receptor agonists like semaglutide and tirzepatide. Carriers of the risk allele at TCF7L2 have a blunted physiological incretin effect but still respond to pharmacological GLP-1 agonism because the receptor itself remains intact.

4.6 Insulin signaling and peripheral sensitivity

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
IRS1	rs2943641	near-gene C>T	C allele (ancestral) is PROTECTIVE — higher IRS1 expression, better insulin signaling, $p < 10^{-20}$ (Rung, Nat Genet 2009)	Tyrosine-phosphorylated scaffold; PI3K
IRS1	rs2972143	intronic	Second IRS1 signal; smaller effect	PI3K recruitment
INSR	rs1799816	intronic	Modest insulin resistance association	Tyrosine kinase receptor
PIK3R1	rs706713	intronic	Insulin signaling modulation	PI3K regulatory subunit
AKT2	rs11879191	intronic	Rare coding variants cause insulin resistance syndromes	Ser/Thr kinase; GLUT4 trafficking
SLC2A4	rs5418	promoter G>A	Reduced GLUT4 expression; modestly impaired insulin-stimulated glucose uptake	Insulin-responsive glucose transporter
SLC2A4	rs5435	synonymous	GLUT4 expression modifier	Glucose transporter

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
TBC1D4	p.Arg684Ter	founder nonsense	Greenlandic Inuit founder; homozygotes have OR ≈ 10 for T2D (Moltke, Nature 2014) — largest common T2D effect known	RAB-GAP; GLUT4 translocation

This category controls peripheral glucose disposal and is where insulin sensitizers (metformin, TZDs, exercise, weight loss) act. The IRS1 rs2943641 C allele is one of the few clearly protective common variants in T2D biology and identifies individuals with intrinsically efficient insulin signaling. The TBC1D4 founder variant is an outlier — a rare nonsense mutation reaching high frequency in an isolated population — but a mechanistic demonstration that GLUT4 trafficking is rate-limiting for postprandial glucose disposal.

4.7 Hepatic glucose output

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
GCKR	rs1260326 (reprised)	P446L C>T	Hepatic glucokinase regulation; see 4.2 for full annotation	Fructose-6-P sensing
G6PC2	rs560887 (reprised)	intronic	Largest fasting glucose effect; beta-cell and hepatic glucose-6-phosphatase	Glucose-6-phosphatase
PCK1	rs2179706	near-gene	Cytosolic PEPCK; rate-limiting for gluconeogenesis	GTP, Mn^{2+}
PPP1R3B	rs9987289	near-gene	Hepatic glycogen synthesis; pleiotropic with lipids	Protein phosphatase-1 regulatory subunit
FOXO1	rs17446614	intronic	Transcription factor for gluconeogenic genes; insulin-suppressed via AKT	AKT phosphorylation; 14-3-3 binding
CREB3L2	rs6947345	intronic	Endoplasmic reticulum stress transcription factor; T2D signal	bZIP transcription

Hepatic glucose output sets fasting plasma glucose. GCKR and G6PC2 are both reprised here because their function is distributed across hepatic and beta-cell compartments. Pharmacological targeting of this node is dominated by metformin (AMPK/lysosomal mechanism), imeglimin (mitochondrial), and — historically — glucagon receptor antagonism.

4.8 Adiposity, adipokines, and lipid crosstalk

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
PPARG	rs1801282	Pro12Ala C>G	Ala allele (minor) is PROTECTIVE; OR ≈ 0.86 for T2D (Altshuler, Nat Genet 2000) — first reproducible T2D variant	PPAR-gamma; TZD target
FTO	rs9939609	intronic T>A	A allele raises BMI ~0.39 kg/m²/allele and T2D OR ≈ 1.27, $p < 10^{-50}$ (Frayling, Science 2007). Acts via IRX3/IRX5 in adipocyte progenitors (Claussnitzer, NEJM 2015)	Adipocyte differentiation; beige-to-white switch
FTO	rs8050136	intronic	In LD with rs9939609	Adipocyte differentiation
MC4R	rs17782313	near-gene	Obesity and T2D risk; satiety signaling. Rare LOF causes severe obesity	Melanocortin signaling
ADIPOQ	rs17300539	-11391 G>A	A allele PROTECTIVE — higher adiponectin (Vasseur, HMG 2002)	Adiponectin secretion
ADIPOQ	rs266729	-11377 C>G	G allele lowers adiponectin and raises T2D risk	Adiponectin secretion
ADIPOQ	rs1501299	+276 G>T	T allele modestly reduces adiponectin	Adiponectin secretion
LEPR	rs1137101	Q223R	Leptin receptor function; obesity and insulin resistance associations	Leptin signaling; JAK2/STAT3
IRS2	rs1865434	intronic	Insulin receptor substrate 2; beta-cell and hepatic signaling	PI3K recruitment

This category captures obesity-driven T2D and the adipose endocrine axis. PPARG Pro12Ala is historically the first reproducible T2D common variant and the molecular target of the TZD class; carriers of the protective Ala allele have enhanced PPAR-gamma activity and better adipocyte insulin sensitivity. FTO was for a decade the strongest obesity GWAS signal; the Claussnitzer work showing its effect runs through IRX3/IRX5 in adipocyte progenitors remains the cleanest mechanistic deconvolution of a GWAS locus.

4.9 Circadian and meal-timing regulation

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
MTNR1B	rs10830963 (reprised)	intronic C>G	See 4.1; inhibits nocturnal insulin via enhanced melatonin signaling	Melatonin signaling; beta-cell
CRY2	rs11605924	intronic	Fasting glucose (Dupuis, Nat Genet 2010)	Circadian repressor
PER2	rs7221412	intronic A>G	Altered meal-timing glucose response; poorer evening glucose tolerance	Circadian period

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
CLOCK	rs1801260	3' UTR T>C	Metabolic syndrome and weight-loss response associations	Master circadian transcription
ARNTL (BMAL1)	rs7950226	intronic	T2D and hypertension associations	Circadian heterodimer partner of CLOCK

The circadian system sets diurnal glucose tolerance. Evening glucose tolerance is physiologically worse than morning; carriers of risk alleles at MTNR1B and PER2 amplify this asymmetry. The clinical implications are twofold: front-loaded carbohydrate intake earlier in the day aligns with the intact morning secretion window, and high-dose evening melatonin supplementation — popular for sleep — can further suppress nocturnal insulin secretion in MTNR1B G-allele carriers.

4.10 Vitamin D–glucose axis

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
CYP2R1	rs10741657	intronic A>G	G allele lowers 25(OH)D by ~0.06 SD/allele, $p < 10^{-40}$ (Ahn, HMG 2010; Jiang, Nat Commun 2018, n=417,580)	NADPH, heme; 25-hydroxylase
GC	rs2282679	intronic	Strongest 25(OH)D GWAS signal; vitamin D binding protein levels	Vitamin D transport
VDR	rs2228570	FokI T>C	Short (f) isoform is MORE transcriptionally active — FF carriers get stronger downstream VDR signal (Uitterlinden, Gene 2004)	1,25-$(OH)_2$D; RXR heterodimer
VDR	rs1544410	BsmI G>A	3' UTR LD block; associations with bone and metabolic phenotypes	1,25-$(OH)_2$D signaling
VDR	rs7975232	ApaI	3' UTR LD block	1,25-$(OH)_2$D signaling

Beta cells express VDR, and 1,25-$(OH)_2$D upregulates insulin gene transcription. The D2d randomized trial (Pittas, NEJM 2019) tested 4000 IU/day vitamin D3 in prediabetes and missed its primary endpoint, but suggested benefit in vitamin D-insufficient subgroups. CYP2R1 rs10741657 is the rate-limiting 25-hydroxylase variant and the strongest non-binding-protein determinant of serum 25(OH)D. VDR FokI counterintuitively favors the short 'f' isoform for downstream transcriptional activity.

4.11 Mitochondrial function and oxidative stress

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
SOD2	rs4880	V16A T>C	Ala allele has less efficient mitochondrial import, reducing MnSOD activity (Sutton, Pharmacogenetics 2003)	Mn^{2+}; mitochondrial superoxide dismutase

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
GPX1	rs1050450	P198L C>T	Leu allele has reduced glutathione peroxidase activity	Selenium; glutathione
UCP2	rs659366	-866G>A	Promoter variant affecting UCP2 expression and glucose-stimulated insulin secretion	Inner mitochondrial membrane
UCP2	rs660339	Ala55Val	Modest T2D association	Uncoupling protein
NDUFB6	rs540467	intronic	Mitochondrial Complex I subunit; age-dependent muscle insulin resistance	Complex I; NADH dehydrogenase

Beta cells and skeletal muscle are both vulnerable to mitochondrial oxidative stress, and glucotoxicity is mediated in part by mitochondrial ROS. SOD2 V16A is the best-studied variant at this node; the Ala allele product is imported into mitochondria less efficiently, producing intermediate mitochondrial antioxidant capacity. This becomes mechanistically relevant for imeglimin, whose molecular target is the mitochondrial permeability transition pore and which depends on functional mitochondrial antioxidant defense.

4.12 Inflammation and metabolic stress

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
IL6	rs1800795	-174G>C	C allele associated with lower IL-6 production in most studies (Fishman, JCI 1998); direction is population-dependent	IL-6; JAK2-STAT3
TNF	rs1800629	-308G>A	A allele associated with higher TNF-alpha expression	TNF-alpha signaling
CRP	rs3091244	triallelic	Baseline CRP modulator	Acute phase response
CRP	rs1205	3' UTR	CRP levels; cardiometabolic risk correlate	Acute phase response
IL1B	rs16944	-511 C>T	IL-1beta expression modulator	NLRP3 inflammasome
IL10	rs1800896	-1082 A>G	Anti-inflammatory cytokine expression	IL-10 signaling; STAT3

Chronic low-grade inflammation impairs IRS1-mediated insulin signaling and is one of the shared substrates between obesity and T2D. This category overlaps substantially with the inflammation and immune pathway reference; here it is included only in its metabolic-stress context. Most effects on T2D risk via this node are modest individually.

4.13 Pharmacogenomics of antidiabetic drugs

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
SLC22A1 (OCT1)	rs622342	intronic A>C	C allele reduces hepatic uptake of metformin and imeglimin	Organic cation transporter
SLC22A1	rs12208357	R61C	Reduced-function allele; lowers hepatic drug uptake (Shu, JCI 2007)	Organic cation transporter
SLC22A1	rs72552763	M420del	Reduced-function deletion (Tzvetkov, CPT 2009)	Organic cation transporter
SLC47A1 (MATE1)	rs2289669	intronic	Metformin renal efflux; modest HbA1c response effect	Multidrug extrusion
ATM	rs11212617	intronic	Metformin glycemic response (MetGen, Nat Genet 2011)	DNA damage kinase; AMPK crosstalk
CYP2C9	*2 (rs1799853)	R144C	Reduced sulfonylurea clearance	CYP2C9; heme
CYP2C9	*3 (rs1057910)	I359L	Markedly reduced sulfonylurea clearance	CYP2C9; heme
KCNJ11	E23K (reprised)	C>T	Sulfonylurea response modifier (same KATP channel they target)	Sulfonylurea receptor
GLP1R	rs6923761 (reprised)	G168S	Differential response to GLP-1 agonists	Gs/cAMP

This category is where genetic information most directly informs drug selection. OCT1 reduced-function variants lower hepatic exposure to metformin and imeglimin, both of which depend on OCT1-mediated uptake for their pharmacological effect. CYP2C9 poor-metabolizer alleles raise sulfonylurea exposure and hypoglycemia risk — relevant if any sulfonylurea is ever used. The ATM rs11212617 locus was the first metformin response GWAS signal (MetGen, Nat Genet 2011).

4.14 Latent autoimmune diabetes in adults (LADA)

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
HLA-DQB1	rs9273368	intergenic A>G	Lead LADA SNP in Cousminer GWAS; tags DR4-DQ8/DR3-DQ2 risk haplotypes. OR ≈ 3.30 in highest GADA-titer tertile, p = 1.89×10^{-47} (Cousminer, Diabetes Care 2018)	MHC class II antigen presentation
HLA-DQA1	rs2187668	intronic C>T	Tags HLA-DR3-DQ2 (DQA1*05:01-DQB1*02:01) haplotype; T1D and LADA risk; also celiac disease	MHC class II
HLA-DQB1	rs7454108	intergenic	Tags HLA-DR4-DQ8	MHC class II

Gene	rsID	Variant	Functional consequence	Cofactor / pathway node
			(DQB1*03:02) haplotype; primary T1D risk allele	
PTPN22	rs2476601	R620W C>T	T allele (Trp620) is the canonical autoimmunity risk variant; LADA OR ≈ 1.5–1.9 (Petrone, Diabetes Care 2008). Causes gain-of-function in lymphocyte tyrosine phosphatase, altering T-cell and B-cell receptor signaling thresholds	T/B cell receptor signaling
INS	rs689	VNTR proxy A>T	Tags the INS VNTR class I (short) allele, associated with reduced thymic insulin expression and impaired central tolerance to insulin; LADA and T1D risk	Insulin gene transcription / thymic tolerance
SH2B3 (LNK)	rs3184504	R262W C>T	Pleiotropic autoimmune locus (T1D, RA, celiac, hypertension, MPN). T allele LADA risk; affects cytokine signaling adaptor in lymphocytes (Cousminer 2018)	JAK/STAT scaffold; cytokine signaling
PFKFB3	rs9884207 region	intronic	Novel LADA-specific signal in Cousminer GWAS; sits at intersection of glycolysis regulation, insulin signaling, and inflammation — biologically positioned between T1D and T2D	6-phosphofructo-2-kinase; glycolytic regulator
CTLA4	rs3087243	CT60 G>A	T1D and autoimmune locus (Graves, AIH, RA); modest LADA association in candidate-gene studies	T-cell coinhibitory receptor; ipilimumab target
IL2RA	rs41295121	intronic	T1D risk locus; IL-2 receptor alpha chain (CD25); regulatory T-cell function. Modest LADA signal in subgroup analyses	Treg / IL-2 signaling
BACH2	rs11755527	intronic G>C	T1D and autoimmune locus; transcriptional repressor in B and T cells; Treg differentiation	B/T cell transcription
IFIH1 (MDA5)	rs1990760	A946T A>G	Cytosolic dsRNA sensor; T1D risk and LADA candidate locus	Type I interferon induction

LADA sits at the intersection of T1D and T2D genetics. The Cousminer 2018 GWAS established that the four genome-wide-significant LADA loci (HLA, PTPN22, INS, SH2B3) are all classical T1D loci, while T2D loci including TCF7L2 also contribute. The HLA class II signal is by far the largest, with an effect size that exceeds any common T2D variant by an order of magnitude. The clinical relevance is that an individual with strong LADA-flavored genetics presenting as adult-onset diabetes warrants anti-GAD antibody testing, since a positive result

fundamentally changes treatment trajectory: faster progression to insulin requirement, avoidance of beta-cell-exhausting agents like sulfonylureas, and consideration of beta-cell-preserving strategies. PTPN22 R620W is also a major signal in the inflammation and immune pathway — its effects are not confined to glucose biology.

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

Category	Key genes	Cofactors / substrates	Supplement / dietary targets
Beta-cell transcription	TCF7L2, HHEX, HNF1A/B/4A, MTNR1B	Wnt, GLP-1, melatonin	Adequate sleep timing; avoid high-dose evening melatonin
Glucose sensing (GCK axis)	GCK, GCKR, G6PC2, ADCY5	Mg^{2+}, ATP, fructose-6-P	Magnesium (malate, glycinate, threonate); limit fructose
KATP channel & exocytosis	KCNJ11, ABCC8, KCNQ1, SLC30A8	ATP/ADP, Zn^{2+}, Ca^{2+}	Zinc bisglycinate; dietary zinc
Proinsulin processing	CDKAL1, WFS1, IGF2BP2	Fe-S cluster, ER Ca^{2+}	Iron sufficiency without excess; ER stress reduction via caloric control
Incretin axis	GLP1R, GIPR, DPP4	cAMP, Gs signaling	GLP-1 pharmacology; protein-forward meals stimulate endogenous GLP-1
Insulin signaling	IRS1, INSR, AKT2, SLC2A4, TBC1D4	Mg^{2+}, chromium, myo-inositol	Magnesium; myo-inositol (2–4 g); chromium picolinate (200–400 mcg)
Hepatic glucose output	GCKR, G6PC2, PCK1, FOXO1	Mn^{2+}, GTP, AKT signaling	Manganese (trace); caloric/fasting protocols for hepatic insulin
Adiposity & adipokines	PPARG, FTO, ADIPOQ, MC4R	Fatty acids, PPAR ligands	Omega-3 (EPA/DHA); resistance training; body composition
Circadian	MTNR1B, CRY2, PER2, CLOCK	Melatonin, light exposure	Morning light; front-loaded carbohydrate timing; caution with evening melatonin
Vitamin D axis	CYP2R1, GC, VDR	NADPH, heme, 1,25-$(OH)_2$D	Vitamin D3 (dose to 25(OH)D 40–60 ng/mL); vitamin K2 adjunct

Category	Key genes	Cofactors / substrates	Supplement / dietary targets
Mitochondrial & oxidative	SOD2, GPX1, UCP2	Mn^{2+}, Se, glutathione, CoQ10	Manganese; selenium (100–200 mcg); ubiquinol; NAC; ergothioneine
Inflammation	IL6, TNF, CRP, IL1B	Arachidonic/EPA balance	Omega-3; polyphenols; exercise
Pharmacogenomics	SLC22A1, SLC47A1, ATM, CYP2C9, GLP1R	Drug-specific	Drug selection; dose adjustment
LADA (autoimmune diabetes)	HLA-DQB1/DQA1, PTPN22, INS, SH2B3, PFKFB3	MHC II antigen presentation; T-cell signaling	Anti-GAD testing if multiple risk alleles; avoid sulfonylureas; consider early insulin-sparing therapy

6. Complete SNP Lookup Table

All SNPs catalogued in Section 4, consolidated for reference. GRCh38 coordinates are provided for positional VCF lookup when rsID annotation is incomplete.

Gene	rsID	Variant	GRCh38 coord	Key note
TCF7L2	rs7903146	C>T	chr10:112998590	Strongest T2D signal
TCF7L2	rs12255372	G>T	chr10:113049143	LD with rs7903146
HHEX	rs1111875	T>C	chr10:92703125	Beta-cell development
HHEX	rs7923837	A>G	chr10:92708951	Second HHEX signal
PROX1	rs340874	C>T	chr1:213985913	Fasting glucose
HNF1A	rs1169288	I27L	chr12:120978565	MODY3 common variant
HNF1B	rs4430796	A>G	chr17:37741642	MODY5 / prostate pleiotropy
HNF4A	rs4812829	A>G	chr20:44355634	MODY1 common variant
MTNR1B	rs10830963	C>G	chr11:92975544	Nocturnal insulin suppression
MTNR1B	rs1387153	C>T	chr11:92940662	Secondary MTNR1B
GCK	rs1799884	G>A	chr7:44196069	Promoter; fasting

Gene	rsID	Variant	GRCh38 coord	Key note
				glucose
GCK	rs4607517	G>A	chr7:44229068	Fasting glucose
GCKR	rs1260326	C>T (P446L)	chr2:27508073	Pleiotropic glucose/lipid/urate
G6PC2	rs560887	C>T	chr2:168906638	Largest fasting glucose effect
ADCY5	rs11708067	A>G	chr3:123346931	Incretin-stimulated insulin
DGKB	rs2191349	T>G	chr7:14898282	Fasting glucose
MADD	rs7944584	A>T	chr11:47312130	Proinsulin conversion
SLC2A2	rs11920090	A>T	chr3:170996030	GLUT2 glucose sensor
KCNJ11	rs5219	C>T (E23K)	chr11:17387083	Canonical T2D variant
KCNJ11	rs5215	T>C	chr11:17388025	LD with E23K
ABCC8	rs757110	A>C (S1369A)	chr11:17392498	SUR1 subunit
KCNQ1	rs2237892	C>T	chr11:2818521	East Asian T2D signal
KCNQ1	rs231362	T>C	chr11:2706351	European KCNQ1 signal
CACNA1D	rs312457	A>G	chr3:53545182	L-type Ca channel
SLC30A8	rs13266634	C>T (R325W)	chr8:117172544	ZnT8; insulin crystallization
CDKAL1	rs7756992	A>G	chr6:20679478	tRNA modification / proinsulin
CDKAL1	rs10946398	A>C	chr6:20661250	Second CDKAL1 signal
IGF2BP2	rs4402960	G>T	chr3:185793899	Common T2D variant
WFS1	rs10010131	G>A	chr4:6292915	Wolfram gene; ER Ca^{2+}
GLP1R	rs10305492	G>A (A316T)	chr6:39048727	Protective missense
GLP1R	rs6923761	G>A (G168S)	chr6:39046794	GLP-1 agonist response
GIPR	rs10423928	T>A (E354Q)	chr19:45668748	Incretin response
DPP4	rs6741949	C>G	chr2:162890717	DPP-4 activity

Gene	rsID	Variant	GRCh38 coord	Key note
IRS1	rs2943641	C>T	chr2:226229029	Protective C allele
IRS1	rs2972143	A>G	chr2:226229324	Second IRS1 signal
INSR	rs1799816	T>C	chr19:7117689	Modest IR association
AKT2	rs11879191	C>T	chr19:40231604	Rare LOF causes IR syndromes
SLC2A4	rs5418	G>A	chr17:7283866	GLUT4 promoter
SLC2A4	rs5435	T>C	chr17:7285987	GLUT4 synonymous
TBC1D4	rs61736969	p.Arg684Ter	chr13:75370568	Greenlandic founder; OR≈10
PCK1	rs2179706	C>T	chr20:57563949	PEPCK; gluconeogenesis
PPP1R3B	rs9987289	G>A	chr8:9325633	Hepatic glycogen
FOXO1	rs17446614	G>A	chr13:40562335	Gluconeogenic TF
PPARG	rs1801282	C>G (Pro12Ala)	chr3:12351626	Protective Ala allele
FTO	rs9939609	T>A	chr16:53786615	Largest BMI signal
FTO	rs8050136	C>A	chr16:53782363	LD with rs9939609
MC4R	rs17782313	T>C	chr18:60161902	Satiety / obesity
ADIPOQ	rs17300539	G>A	chr3:186841685	Protective adiponectin-raising
ADIPOQ	rs266729	C>G	chr3:186841428	Risk allele
ADIPOQ	rs1501299	G>T	chr3:186853103	Modest reduction
LEPR	rs1137101	A>G (Q223R)	chr1:65592830	Leptin receptor
CRY2	rs11605924	C>A	chr11:45847148	Fasting glucose
PER2	rs7221412	A>G	chr2:238286378	Evening glucose tolerance
CLOCK	rs1801260	T>C	chr4:55435202	Metabolic syndrome
ARNTL	rs7950226	G>A	chr11:13299303	BMAL1; T2D/HTN

Gene	rsID	Variant	GRCh38 coord	Key note
CYP2R1	rs10741657	A>G	chr11:14893332	25(OH)D production
GC	rs2282679	A>C	chr4:72608383	VDBP levels
VDR	rs2228570	T>C (FokI)	chr12:47879112	Transcriptional efficiency
VDR	rs1544410	G>A (BsmI)	chr12:47845054	3' UTR LD
VDR	rs7975232	A>C (ApaI)	chr12:47845105	3' UTR LD
SOD2	rs4880	T>C (V16A)	chr6:159692840	Mitochondrial import
GPX1	rs1050450	C>T (P198L)	chr3:49357401	GPX activity
UCP2	rs659366	G>A	chr11:74002016	Promoter -866
UCP2	rs660339	C>T (Ala55Val)	chr11:74004102	Coding variant
IL6	rs1800795	G>C	chr7:22727026	-174 promoter
TNF	rs1800629	G>A	chr6:31575254	-308 promoter
CRP	rs3091244	triallelic	chr1:159712443	Baseline CRP
SLC22A1	rs622342	A>C	chr6:160155670	OCT1 activity
SLC22A1	rs12208357	C>T (R61C)	chr6:160139851	Reduced OCT1
SLC22A1	rs72552763	del (M420del)	chr6:160144554	Reduced OCT1
SLC47A1	rs2289669	G>A	chr17:19571762	MATE1 efflux
ATM	rs11212617	A>C	chr11:108410947	Metformin response
CYP2C9	rs1799853	C>T (*2)	chr10:94942290	Reduced sulfonylurea clearance
CYP2C9	rs1057910	A>C (*3)	chr10:94981296	Reduced sulfonylurea clearance
HLA-DQB1	rs9273368	A>G	chr6:32658525	Lead LADA SNP; HLA class II
HLA-DQA1	rs2187668	C>T	chr6:32605884	Tags DR3-DQ2 haplotype

Gene	rsID	Variant	GRCh38 coord	Key note
HLA-DQB1	rs7454108	T>C	chr6:32689478	Tags DR4-DQ8 haplotype
PTPN22	rs2476601	G>A (R620W)	chr1:113834946	Canonical autoimmunity variant
INS	rs689	A>T	chr11:2160994	INS VNTR class proxy
SH2B3	rs3184504	C>T (R262W)	chr12:111446804	Pleiotropic autoimmune
PFKFB3	rs9884207	intronic	chr10:6189617	LADA-specific (Cousminer 2018)
CTLA4	rs3087243	G>A (CT60)	chr2:203874196	T-cell coinhibitory
IL2RA	rs41295121	intronic	chr10:6056986	Treg / IL-2 signaling
BACH2	rs11755527	G>C	chr6:90267049	B/T cell transcription
IFIH1	rs1990760	A>G (A946T)	chr2:162267541	Type I IFN sensor

Note: GRCh38 coordinates are approximate consensus values from dbSNP and Ensembl build 110; verify against the target VCF reference assembly before positional queries.

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