Glycation

Genetic Pathway Reference

8 Functional Categories • ~29 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 glycation pathway, the genes that regulate it, the well-studied common variants in those genes, the cofactors each enzyme requires, and the supplement targets that map to each cofactor and pathway node. 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 confer small individual effects (odds ratios in the 1.1–1.4 range), with the notable exception of AGER rs2070600, which behaves as a large-effect cis-pQTL (GWAS $p \approx 10^{-52}$ for soluble RAGE level). Clinical significance arises from cumulative patterns and gene–environment interactions, particularly with glycemic control, dietary AGE intake, and oxidative stress.

2. Pathway Biology

2.1 What glycation is

Glycation is the non-enzymatic covalent attachment of a reducing sugar (glucose, fructose, ribose) or — more damagingly — a reactive α-oxoaldehyde (methylglyoxal, glyoxal, 3-deoxyglucosone) to the free amino groups of proteins, lipids, or nucleic acids. It is distinct from glycosylation, which is enzyme-catalyzed and tightly regulated. Glycation is a slow chemical accident under normoglycemia and a major source of cumulative tissue damage under hyperglycemia, oxidative stress, or impaired carbonyl detoxification.

2.2 The three stages

The reaction proceeds in three kinetic stages. First, a Schiff base forms within minutes when an amine group attacks the carbonyl carbon of a sugar, producing a labile aldimine that is freely reversible. Second, over hours to days, the Schiff base undergoes Amadori rearrangement to a stable ketoamine; HbA1c is the canonical Amadori product, formed on the N-terminal valine of hemoglobin's β-chain. Third, over weeks to years, Amadori products undergo oxidation, fragmentation, and crosslinking to yield a heterogeneous family of advanced glycation end products (AGEs). The third stage is essentially irreversible by spontaneous chemistry; only enzyme-mediated repair (by fructosamine-3-kinase) or proteolysis can remove early adducts.

2.3 The methylglyoxal shortcut

Methylglyoxal (MG) is the most reactive endogenous glycating agent — roughly 20,000-fold more reactive than glucose itself. It is generated continuously from the triose phosphates dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate (G3P) that leak out of glycolysis. Under hyperglycemia, glycolytic flux exceeds the capacity of downstream enzymes, triose phosphates accumulate, and MG production rises sharply. MG attacks arginine and lysine residues to form hydroimidazolone adducts (MG-H1) and carboxyethyl-lysine (CEL), and crosslinks proteins to form MOLD (methylglyoxal lysine dimer) and related structures. Because MG is so reactive, the dedicated detoxification system — the glyoxalase pathway — is the dominant defense against glycation in most tissues.

2.4 The AGE-RAGE inflammatory axis

Once AGEs form, they bind a transmembrane signaling receptor, the Receptor for Advanced Glycation End-products (RAGE, encoded by AGER), which is expressed on endothelial cells, monocytes/macrophages, vascular smooth muscle, podocytes, retinal pericytes, neurons, and microglia. RAGE engagement activates DIAPH1 (the cytoplasmic adaptor), NADPH oxidase (Nox), and the NF-κB pathway, producing chronic low-grade inflammation, ROS amplification, and expression of pro-inflammatory cytokines, adhesion molecules, and tissue factor. Soluble RAGE (sRAGE) is generated by alternative splicing or by ADAM10/MMP9-mediated ectodomain shedding; it acts as a circulating decoy receptor that absorbs AGE ligands without signaling. Lower sRAGE levels are therefore associated with greater AGE-RAGE signaling and increased cardiovascular and renal disease risk.

2.5 Brownlee's unifying hypothesis

Michael Brownlee's 2001 unifying hypothesis (Nature 414:813–820) places glycation at the center of a five-pathway hub of hyperglycemia-induced damage: increased polyol flux (aldose reductase, AKR1B1), increased AGE formation, protein kinase C activation, increased hexosamine flux (via fructose-6-phosphate diversion), and overproduction of mitochondrial superoxide. All five branches are downstream of the same upstream cause: triose phosphate accumulation when transketolase (the rate-limiting thiamine-dependent enzyme of the pentose phosphate pathway) cannot keep up. This is why benfotiamine, a lipid-soluble thiamine prodrug, blocks all four hyperglycemic damage pathways simultaneously by activating transketolase and shunting triose phosphates back into the pentose phosphate pathway (Hammes et al., Nat Med 2003).

2.6 Why glycation matters across diseases

Cumulative AGE accumulation is implicated in diabetic microvascular complications (retinopathy, nephropathy, neuropathy), atherosclerosis (AGE-modified LDL is more atherogenic; collagen crosslinking stiffens arteries), Alzheimer's disease (AGEs accumulate in

plaques and tangles; AGER rs2070600 risk allele linked to CA1 atrophy), Parkinson's disease (RAGE-mediated microglial inflammation), skin aging (collagen and elastin crosslinking), cataracts (lens crystallin glycation), and chronic kidney disease (mesangial GLUT1 expression and AGE accumulation in glomerular basement membrane). Dietary AGEs from highly processed and high-temperature-cooked foods contribute to circulating AGE pool, and several large observational studies link dietary AGE restriction to improved inflammatory markers.

3. Functional Categories

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

#	Category	Function	Key genes
1	Glucose entry into cells	Substrate delivery; controls intracellular glucose load in cells lacking autoregulation	SLC2A1 (GLUT1)
2	Polyol pathway	Reduces glucose to sorbitol, depletes NADPH, produces fructose and 3-DG	AKR1B1, SORD
3	MG generation & detoxification	Detoxifies the most reactive endogenous glycating agent; repairs early Amadori adducts	GLO1, HAGH (GLO2), FN3K, FN3KRP
4	Pentose phosphate shunt	Diverts triose phosphates away from MG formation; thiamine-dependent	TKT, TKTL1, SLC19A2, TPK1
5	AGE receptor signaling	Translates AGE accumulation into NF-κB-driven inflammation; sRAGE acts as decoy	AGER (RAGE), DIAPH1
6	Antioxidant defense	Limits ROS amplification by AGE-RAGE; protects against glycoxidation	SOD2, GPX1, CAT
7	NRF2 / glutathione synthesis	Master transcriptional regulator of GLO1, GCLC, NQO1, HMOX1; controls GSH supply	NFE2L2 (NRF2), KEAP1, GCLC, GCLM
8	Collagen / matrix turnover	Modulates how long AGE-modified structural proteins persist in tissues	MMP1, MMP9

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) the enzyme requires. Effect sizes and GWAS p-values are noted where they are well-established. The single strongest individual signal in this entire pathway is AGER rs2070600 (Lim et al. 2017, $p = 1.21 \times 10^{-52}$ for plasma sRAGE), which is also one of the most replicated cardiometabolic protein QTLs known.

4.1 Category 1 — Glucose entry into cells

GLUT1 is the dominant constitutive glucose transporter at the blood–brain barrier, blood–retinal barrier, erythrocyte membrane, and on glomerular mesangial cells. Cells expressing GLUT1 cannot downregulate glucose uptake when extracellular glucose rises, so GLUT1 expression level directly controls intracellular glycation pressure in these tissues. SLC2A1 polymorphisms have been associated with diabetic nephropathy and retinopathy across multiple populations and meta-analyses.

Gene	rsID	Variant	Functional consequence	Cofactors
SLC2A1	rs841853	XbaI G>T (intronic)	T allele (XbaI−) increases mesangial GLUT1 expression; ~2× DN risk in T1DM (Hodgkinson 2001)	None
SLC2A1	rs1385129	HaeIII C>T (synonymous, exon 2)	T allele has enhancer/promoter activity in HEK-293T; risk allele in Tunisian and Kurdish DN cohorts (Kulin 2022)	—
SLC2A1	rs841847	Enh2-1 C>T (intron 2)	Functional enhancer; T allele decreases erythrocyte GLUT1; mixed direction in DN	—
SLC2A1	rs841848	Enh2-2 G>A (intron 2)	Paired enhancer with rs841847; minor allele increases GLUT1 expression	—
SLC2A1	rs3820589	3' region	A allele protective for incipient DN in Brazilian T1DM (Marques 2015, OR 0.36)	—

4.2 Category 2 — Polyol pathway

When intracellular glucose exceeds the Km of hexokinase (~5 mM), aldose reductase (AKR1B1) reduces glucose to sorbitol using NADPH as the redox cofactor. Sorbitol dehydrogenase (SORD) then oxidizes sorbitol to fructose using NAD^+. Two consequences are damaging: NADPH depletion impairs glutathione regeneration (GSSG → GSH requires NADPH via glutathione reductase), and fructose feeds into fructose-3-phosphate → 3-deoxyglucosone, a powerful glycating agent.

Gene	rsID	Variant	Functional consequence	Cofactors
AKR1B1	rs759853	C(−106)T promoter	T allele increases promoter activity, raises AR expression; CC associated with DR risk in T1DM (meta-analysis OR 2.07; Kaur 2016); allele direction differs by population/diabetes type	NADPH
AKR1B1	rs9640883	Intronic	Associated with DR ($p = 5 \times 10^{-4}$, Abhary 2010); also associated with younger age at diabetes onset	—
AKR1B1	(CA)n / Z−2 / Z+2	5' microsatellite	Z−2 allele = high AR expression and DN risk; Z+2 = protective; oldest reported AR	—

Gene	rsID	Variant	Functional consequence	Cofactors
			variant (Shah 1998)	
SORD	Various	Sorbitol dehydrogenase	LoF mutations cause hereditary neuropathy (sorbitol accumulation); common variants less well characterized	NAD^+

4.3 Category 3 — Methylglyoxal generation and detoxification

The glyoxalase system (GLO1 + GLO2 + reduced glutathione) is the primary defense against methylglyoxal. GLO1 catalyzes the GSH-dependent conversion of MG to S-D-lactoylglutathione, which GLO2 then hydrolyzes to D-lactate, regenerating GSH. The system absolutely requires GSH as a co-substrate and Zn^{2+} at the GLO1 active site. Fructosamine-3-kinase (FN3K) is a separate, ATP-dependent deglycation enzyme that phosphorylates Amadori products on the third carbon of the sugar moiety, destabilizing them and causing them to detach from proteins before they progress to AGEs.

Gene	rsID	Variant	Functional consequence	Cofactors
GLO1	rs4746 (=rs2736654)	A332C, p.Glu111Ala	A allele encodes Glu111, altered conformation; decreased activity in some studies (Pierluigi 2005); functional impact mixed (Peculis 2013, CODAM 2021 found no effect on activity or MG markers)	GSH; Zn^{2+}
GLO1	rs1130534	T>A	Minor allele significantly decreases GLO1 enzyme activity (Peculis 2013, $p = 1 \times 10^{-3}$)	GSH; Zn^{2+}
GLO1	rs1049346	C>T	Minor allele significantly decreases GLO1 activity (Peculis 2013, $p = 2.6 \times 10^{-5}$); strongest functional GLO1 signal	GSH; Zn^{2+}
FN3K	rs1056534	c.900C>G, exon 6	C allele = higher deglycation, lower HbA1c, later T2DM onset (Mohás 2010, n=1,124); G allele = positive glycation gap (Diabetes 2025)	ATP; Mg^{2+}
FN3K	rs3859206	c.−385A>G promoter	GG = reduced FN3K erythrocyte activity (Delpierre 2006); paired with rs1056534 in functional haplotype	ATP; Mg^{2+}
FN3K	rs2256339	c.−232A>T promoter	TT = better deglycation; AA = worse glycation gap (Diabetes 2025)	ATP; Mg^{2+}

4.4 Category 4 — Pentose phosphate shunt

Transketolase (TKT) catalyzes the non-oxidative branch of the pentose phosphate pathway, transferring 2-carbon ketol fragments between sugars. When fully active, it diverts the triose phosphates G3P and F6P out of glycolysis and into the pentose phosphate pathway, generating

NADPH and ribose-5P and removing the substrate for methylglyoxal formation. TKT activity absolutely requires thiamine pyrophosphate (TPP/ThDP) as cofactor; thiamine status is therefore a critical upstream determinant of glycation pressure. Benfotiamine, a lipid-soluble thiamine prodrug, blocks AGE accumulation in endothelial cells through TKT activation (Hammes 2003).

Gene	rsID	Variant	Functional consequence	Cofactors
TKT	Multiple rare LoF	—	Biallelic LoF causes SDDHD syndrome (short stature, developmental delay, congenital heart defects); common functional SNPs less well characterized	TPP; Mg^{2+} or Ca^{2+}
TKTL1	Various	Transketolase-like 1	Cancer-associated; Warburg-effect linked; common variants poorly characterized	TPP
SLC19A2	Various	Thiamine transporter 1	Rare LoF causes thiamine-responsive megaloblastic anemia (TRMA); common variants modulate thiamine uptake	—
SLC19A3	Various	Thiamine transporter 2	LoF causes biotin-thiamine-responsive basal ganglia disease	—
TPK1	Various	Thiamine pyrophosphokinase 1	Converts free thiamine to TPP, the active cofactor for TKT/PDH/OGDH	ATP; Mg^{2+}

Note: GWAS signal at this category is weaker than mechanistic and pharmacological evidence. The category is included because thiamine sufficiency and TKT activation are the most plausible upstream targets for limiting MG production.

4.5 Category 5 — AGE receptor signaling (RAGE / AGER)

RAGE (encoded by AGER, on chromosome 6p21 within the MHC class III region) is a pattern-recognition receptor whose ligands include AGEs, S100 proteins, HMGB1, amyloid-β, and certain phospholipids. RAGE has no kinase activity; it signals through the cytoplasmic adaptor DIAPH1 to activate Rac1, NADPH oxidase, and NF-κB. Soluble RAGE (sRAGE) is produced by alternative splicing (esRAGE) and by metalloproteinase cleavage of the cell-surface receptor; it acts as a circulating decoy. The genetic determinants of sRAGE are dominated by AGER itself, the strongest of which is rs2070600.

Gene	rsID	Variant	Functional consequence	Cofactors
AGER	rs2070600	G82S (Gly82Ser), missense V-Ig domain	T allele (Ser82) increases ligand-binding affinity, decreases sRAGE ~50%; GWAS p = 1.21×10^{-52} for plasma sRAGE (Lim 2017, n=2,058 + 1,984 replication); HR 1.13 for first MACE in MDC cohort (n=24,640; Sci Rep 2024); also PD risk and AD CA1 atrophy	None

Gene	rsID	Variant	Functional consequence	Cofactors
AGER	rs1800624	−374T>A promoter	A allele alters SP1 binding, raises sRAGE; protective for some vascular outcomes	—
AGER	rs1800625	−429T>C promoter	C allele increases transcription	—
AGER	rs2071288	Intronic	Explains 26% of sRAGE variance in Black ARIC participants; minor allele lowers sRAGE 43% (Selvin 2015)	—
AGER	rs184003	Intron 7 G>T	Mixed disease associations; raised T1DM risk	—
AGER	63-bp deletion	Promoter	Less common; alters expression in some populations	—
DIAPH1	Various	Cytoplasmic RAGE adaptor	Required for RAGE signal transduction; emerging therapeutic target (Schmidt lab); GWAS signals for cardiometabolic outcomes	—

4.6 Category 6 — Antioxidant defense

Glycation and oxidation are tightly coupled — AGE formation produces ROS, and ROS accelerate the autoxidation of Amadori products to AGEs (the "glycoxidation" cycle). Three antioxidant enzymes set the buffer: SOD2 (mitochondrial Mn-superoxide dismutase, the only SOD inside mitochondria), GPX1 (the dominant cytosolic glutathione peroxidase, requiring selenium), and CAT (peroxisomal/cytosolic catalase). Functional polymorphisms in all three modify diabetic complication risk.

Gene	rsID	Variant	Functional consequence	Cofactors
SOD2	rs4880	A16V (Ala16Val), c.47T>C in MTS	Val variant alters targeting peptide structure (β-sheet → α-helix), reducing mitochondrial import 30–40%; VV genotype increases DR risk (meta-analysis OR 1.87, $p < 10^{-4}$), DN risk, and HbA1c	Mn^{2+}
GPX1	rs1050450	Pro198Leu (C599T), exon 2	T allele (Leu) reduces selenium responsiveness and enzyme activity; T allele increased post-transplant DM risk OR 2.14 (Tomas 2010); meta-analysis supports DN association	Selenium; GSH
CAT	rs1001179	−262C>T promoter	T allele generally associated with higher CAT expression; mixed direction in DM cohorts	Iron (heme); NADPH
CAT	rs769217	C>T exon 9 (synonymous)	T allele associated with reduced activity in some cohorts; SOD2 + CAT combined	Iron (heme)

Gene	rsID	Variant	Functional consequence	Cofactors
			risk explored (Sultan 2023)	

Note: The published convention for SOD2 rs4880 alleles is inconsistent across studies. dbSNP reports the SNP as T>C, where C encodes Ala (better mitochondrial import, protective) and T encodes Val (impaired import, risk-associated). The damaging amino acid is Val regardless of nucleotide notation.

4.7 Category 7 — NRF2 / glutathione synthesis

NRF2 (NFE2L2) is a basic-leucine-zipper transcription factor that, when released from its repressor KEAP1, binds the antioxidant response element (ARE) and upregulates roughly 200 cytoprotective genes. Critical NRF2 targets for glycation defense include GLO1 (the methylglyoxal detoxifier), GCLC and GCLM (the rate-limiting subunits of glutathione synthesis), HMOX1 (heme oxygenase), and NQO1 (quinone reductase). NRF2 is therefore the master transcriptional regulator of the entire glycation defense apparatus, and its tone determines basal glyoxalase capacity.

Gene	rsID	Variant	Functional consequence	Cofactors
NFE2L2	rs6721961	−617C>A promoter	A allele decreases NRF2 promoter activity and basal expression; reduced antioxidant response, raised lung disease and DN risk	—
NFE2L2	rs35652124	−653A>G promoter	G allele decreases basal NRF2; modifies multiple disease associations	—
NFE2L2	rs2706110	Intronic	Associated with NRF2 expression in some tissues	—
GCLC	rs17883901	−129C>T promoter	T allele decreases GCLC transcription, lowers cellular glutathione synthesis	Cysteine; ATP
GCLM	rs41303970	−588C>T	T allele decreases GCLM expression, lowers GSH biosynthesis capacity	Cysteine; ATP

4.8 Category 8 — Collagen and matrix turnover

Long-lived structural proteins — type I collagen in skin and arteries, lens crystallin, elastin in arterial wall — are the principal targets of cumulative AGE crosslinking. The persistence of AGE-modified protein depends on turnover rate, which is set by matrix metalloproteinases (MMPs). Polymorphisms that slow collagen turnover prolong AGE residence time. Evidence here is more disease-specific (skin aging, arterial stiffness) than for other categories.

Gene	rsID	Variant	Functional consequence	Cofactors
MMP1	rs1799750	−1607 1G/2G	2G allele creates an Ets binding site, ~2× higher MMP1 transcription, faster collagen turnover	Zn^{2+}
MMP9	rs3918242	−1562 C>T	T allele increases MMP9 transcription;	Zn^{2+}

Gene	rsID	Variant	Functional consequence	Cofactors
			context-dependent effects on tissue remodeling	

5. Cofactor and Supplement Target Map

The table below maps each functional category to the cofactors its enzymes need, and to the supplement(s) that can address those cofactor needs. This is a generic catalog of biochemical relationships, not a personalized recommendation.

Category	Cofactors required	Supplement targets
Glucose entry (GLUT1)	None directly (transporter)	Glycemic control upstream (diet, exercise, metformin)
Polyol pathway (AKR1B1)	NADPH	Glycemic control; aldose reductase inhibitors (epalrestat, where available); supporting NADPH (niacinamide, NMN/NR)
MG detox (GLO1/GLO2)	Reduced glutathione (GSH); Zn^{2+}	NAC and glycine (GSH precursors); liposomal glutathione; zinc; sulforaphane (induces GLO1 via NRF2)
Deglycation (FN3K)	ATP; Mg^{2+}	Magnesium; metabolic support (ATP availability)
Pentose phosphate shunt (TKT)	Thiamine pyrophosphate; Mg^{2+} or Ca^{2+}	Benfotiamine (lipid-soluble, ~5× bioavailability of thiamine HCl); thiamine HCl; magnesium
AGE receptor (RAGE/AGER)	None directly	Reduce dietary AGEs (low-AGE cooking methods); sRAGE-supportive interventions (exercise, weight loss)
Antioxidant defense (SOD2, GPX1, CAT)	Mn^{2+} (SOD2); selenium (GPX1); iron-heme (CAT); GSH	Manganese (cautious dosing); selenium (200 µg/day); GSH precursors
NRF2 / GSH synthesis	Cysteine, glycine, glutamate; ATP	NAC; glycine; sulforaphane (BroccoMax, MyrPro); ALA (also NRF2 inducer)
Collagen turnover	Zn^{2+} (MMPs)	Zinc; vitamin C (collagen synthesis); avoid prolonged MMP inhibition

Note: "Supplement target" means a substance that addresses the relevant biochemistry. It does not mean every person should supplement everything listed. Personalization depends on individual genotype, intake, lab values, and clinical context. Aldose reductase inhibitors (epalrestat) are approved in Japan and India but not in the US/EU; they should not be self-prescribed.

6. Complete SNP Lookup Table

Quick reference for all SNPs catalogued in this document, sorted by gene. Coordinates are GRCh38.

Gene	rsID	GRCh38 position	Category
AGER	rs2070600	6:32184220	RAGE signaling
AGER	rs1800624	6:32183984	RAGE signaling
AGER	rs1800625	6:32183929	RAGE signaling
AGER	rs2071288	6:32184574	RAGE signaling
AGER	rs184003	6:32186058	RAGE signaling
AKR1B1	rs759853	7:134522326	Polyol pathway
AKR1B1	rs9640883	7:134510680	Polyol pathway
CAT	rs1001179	11:34438684	Antioxidant defense
CAT	rs769217	11:34461012	Antioxidant defense
FN3K	rs1056534	17:82077326	Deglycation
FN3K	rs3859206	17:82074338	Deglycation
FN3K	rs2256339	17:82074491	Deglycation
GCLC	rs17883901	6:53497818	NRF2 / GSH
GCLM	rs41303970	1:93892099	NRF2 / GSH
GLO1	rs4746	6:38704066	MG detoxification
GLO1	rs1130534	6:38702115	MG detoxification
GLO1	rs1049346	6:38678710	MG detoxification
GPX1	rs1050450	3:49357401	Antioxidant defense
MMP1	rs1799750	11:102799766	Collagen turnover
MMP9	rs3918242	20:46008586	Collagen turnover
NFE2L2	rs6721961	2:177234223	NRF2 / GSH
NFE2L2	rs35652124	2:177234187	NRF2 / GSH
NFE2L2	rs2706110	2:177230091	NRF2 / GSH
SLC2A1	rs841853	1:42928132	Glucose entry
SLC2A1	rs1385129	1:42926164	Glucose entry
SLC2A1	rs841847	1:42930848	Glucose entry
SLC2A1	rs841848	1:42930684	Glucose entry
SLC2A1	rs3820589	1:42959485	Glucose entry

Gene	rsID	GRCh38 position	Category
SOD2	rs4880	6:159692840	Antioxidant defense

Note on coordinates: GRCh38 positions above are best-effort references compiled from dbSNP (build 156) and Ensembl. Verify against your VCF's contig naming convention ("chr1" vs "1") before running positional lookups. Coordinates for SNPs near gene boundaries can shift by a few base pairs between annotation sources.

7. Bibliography and Source Notes

Primary references used in compiling this document, in approximate order of importance for the genetics of glycation:

- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813–820. The foundational unifying hypothesis paper that places hyperglycemia-driven mitochondrial superoxide and triose phosphate accumulation at the center of all five damage pathways.
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- Lim SC, Dorajoo R, Zhang X, et al. Genetic variants in the receptor for advanced glycation end products (RAGE) gene were associated with circulating soluble RAGE level but not with renal function among Asians with type 2 diabetes: a genome-wide association study. Nephrol Dial Transplant 2017;32:1697–1704. The strongest GWAS signal in this entire pathway: AGER rs2070600 with $p = 1.21 \times 10^{-52}$ for sRAGE.
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- Selvin E, Halushka MK, Rawlings AM, et al. sRAGE and risk of diabetes, cardiovascular disease, and death. Diabetes 2013;62:2116–2121, plus PLOS One 2015 ARIC GWAS of plasma sRAGE — establishing rs2070600 and rs2071288 as ethnic-specific lead SNPs.
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- Abhary S, Burdon KP, Laurie KJ, et al. Aldose reductase gene polymorphisms and diabetic retinopathy susceptibility. Diabetes Care 2010;33:1834–1836. Tag SNP analysis of AKR1B1 in 909 Australian patients.
- Schmidt AM. Receptor for AGE (RAGE) and Mediation of Inflammatory Neurodegeneration. Front Cardiovasc Med 2020;7:37. Comprehensive coverage of RAGE biology, DIAPH1, and disease genetics.
- Schalkwijk CG, Stehouwer CDA. Methylglyoxal, a highly reactive dicarbonyl compound, in diabetes, its vascular complications, and other age-related diseases. Physiol Rev 2020;100:407–461. Authoritative review of MG biology.

Database resources used:

- dbSNP (NCBI, build 156) for rsID-to-coordinate mapping (GRCh38).
- OMIM for inherited metabolic disorders (TKT deficiency / SDDHD #617044, TRMA #249270, glucose transporter type 1 deficiency #606777).
- GWAS Catalog (EBI/NHGRI) for GWAS-associated variant lookups.
- ClinVar for variant pathogenicity classifications.
- Ensembl (release 110) for cross-checking GRCh38 positions.

8. Disclaimer

This document is an educational reference. It does not constitute medical advice, does not establish a clinician–patient relationship, and is not a substitute for individualized evaluation by a qualified healthcare provider. Genetic variants are described at the level of common-population biology; clinical interpretation in any individual depends on the full genetic background, lab measurements, medical history, current medications, and other factors that this document does not address.

Most common variants catalogued here confer small individual effect sizes (odds ratios 1.1–1.4). The exception is AGER rs2070600, which behaves as a large-effect cis-pQTL for plasma soluble RAGE and is one of the most replicated cardiometabolic genetic signals known. Even for rs2070600, the absolute increment in cardiovascular event risk is modest (HR 1.13 in the Malmö cohort). Cumulative significance across the pathway arises from patterns of multiple variants and from interaction with environmental factors (glycemic control, dietary AGE intake, oxidative stress, age, ethnicity, comorbidities).