Genomic Variant Analysis Report

SNP Profile Related to Glycation Pathways & HbA1c Discordance

7 Functional Categories • 24 SNPs Analyzed

Date: April 2026 | Source: Whole Genome Sequencing (60x) | Genome Build: GRCh38

Disclaimer: This report summarizes genetic variants identified in whole genome sequencing data. It is intended to support clinical discussion and is not a diagnostic tool. All interpretations are based on published GWAS literature and should be contextualized with clinical metabolic testing.

Clinical Context: The patient's HbA1c is elevated relative to average glucose as measured by a continuous glucose monitor (CGM) calibrated with fingerprick glucose measurements. This report investigates the genetic basis for this discordance (the "glycation gap") by analyzing variants across seven pathways that influence HbA1c independently of average glucose concentration.

1. Understanding Glycation: The Pathways & Genes Analyzed

HbA1c is widely used as a measure of average glucose over 2–3 months, but it is not a direct glucose measurement. It measures the proportion of hemoglobin molecules that have been glycated — a non-enzymatic chemical reaction in which glucose or other sugars attach to proteins. Multiple biological processes influence HbA1c independently of average glucose concentration. This section describes those processes and the genes that control them.

1.1 What Determines HbA1c?

HbA1c reflects four independent factors: (1) average blood glucose concentration, (2) the rate at which glucose and other sugars attach to hemoglobin (glycation rate), (3) the rate at which glycation is enzymatically reversed (deglycation), and (4) the lifespan of red blood cells, since longer-lived RBCs accumulate more glycation. A person with identical glucose levels but longer-lived red blood cells, faster glycation chemistry, or slower deglycation will have a higher HbA1c. This discordance is termed the "glycation gap."

1.2 Iron Metabolism & Erythropoiesis (TMPRSS6, HFE)

TMPRSS6 (transmembrane serine protease 6, also called matriptase-2) regulates hepcidin, the master hormone controlling iron absorption from the gut and iron recycling from macrophages. By cleaving hemojuvelin on the surface of hepatocytes, TMPRSS6 suppresses hepcidin production, allowing iron to enter circulation. When TMPRSS6 function is reduced, hepcidin levels rise, restricting iron availability. This affects the rate at which new red blood cells are produced and can alter RBC turnover dynamics, indirectly influencing HbA1c.

HFE (homeostatic iron regulator) is a membrane protein that modulates the interaction between transferrin receptor and transferrin, regulating iron uptake from the intestine. The H63D variant mildly increases iron absorption; the more severe C282Y variant causes hereditary hemochromatosis. Iron status affects hemoglobin synthesis, RBC production rate, and the oxidative environment within red blood cells, all of which can influence glycation chemistry.

Additional erythropoiesis genes: EPO (erythropoietin) is the hormone that stimulates RBC production in the bone marrow. BMP2 (bone morphogenetic protein 2) regulates hepcidin expression through the SMAD signaling pathway. SLC30A8 is a zinc transporter primarily studied in beta cells but also associated with HbA1c in GWAS. G6PD (glucose-6-phosphate dehydrogenase) is the key enzyme in the pentose phosphate pathway within RBCs, producing NADPH to protect against oxidative damage; deficiency shortens RBC lifespan and lowers HbA1c.

1.3 Red Blood Cell Membrane Structure (ANK1, SPTA1)

ANK1 (ankyrin-1) is the primary anchor protein of the red blood cell membrane cytoskeleton. It connects the spectrin-actin lattice on the inner surface of the membrane to integral membrane proteins (band 3 and Rh-associated glycoprotein). This connection is essential for maintaining the biconcave disc shape and deformability of RBCs as they navigate through capillaries. Severe ankyrin mutations cause hereditary spherocytosis (shortened RBC lifespan), but common subtle variants can shift average RBC lifespan in either direction.

SPTA1 (spectrin alpha chain 1) encodes one half of the spectrin heterodimer, the flexible rod-shaped protein that forms the lattice underlying the RBC membrane. Spectrin tetramers link to actin filaments and are anchored to the membrane by ankyrin. Together, spectrin and ankyrin determine the mechanical resilience of the red blood cell. Variants in either gene can alter membrane stability and thus RBC survival time in circulation, directly affecting HbA1c accumulation.

Additional RBC biology genes: HK1 (hexokinase-1) catalyzes the first step of glycolysis within red blood cells, controlling intracellular glucose consumption. HBS1L-MYB is an intergenic region that regulates fetal hemoglobin levels and erythropoietic programming. GHR (growth hormone receptor) affects erythropoiesis through IGF-1 signaling.

1.4 Deglycation Enzymes (FN3K, FN3KRP)

FN3K (fructosamine-3-kinase) is a remarkable enzyme that performs enzymatic deglycation — it phosphorylates fructosamines (the early products of glycation on proteins), destabilizing the sugar-protein bond and causing the sugar to detach spontaneously. It acts directly on glycated hemoglobin and other glycated proteins, essentially repairing glycation damage. FN3K is the primary reason that glycation is partially reversible in vivo rather than being purely cumulative.

FN3KRP (fructosamine-3-kinase related protein) is a homologous enzyme with broader substrate specificity. While FN3K acts primarily on fructoselysine residues, FN3KRP can deglycate ribulosamines and other sugar-amino acid adducts, extending the repair system to a wider range of glycation products.

1.5 The Glyoxalase System (GLO1)

GLO1 (glyoxalase 1) is the primary defense enzyme against methylglyoxal, one of the most potent glycating agents in human biology. Methylglyoxal is produced as a spontaneous byproduct of glycolysis — approximately 0.1–0.4% of glycolytic flux generates methylglyoxal from the fragmentation of triose phosphates (dihydroxyacetone phosphate and glyceraldehyde-3-phosphate). Despite being present at micromolar concentrations (roughly 1,000 times lower than glucose), methylglyoxal is approximately 20,000 times more reactive as a glycating agent. It rapidly modifies arginine, lysine, and cysteine residues on proteins, forming

advanced glycation end products (AGEs) such as MG-H1 (methylglyoxal-derived hydroimidazolone).

GLO1 detoxifies methylglyoxal by conjugating it with reduced glutathione (GSH) to form S-D-lactoylglutathione, which is then converted to D-lactate by glyoxalase 2 (GLO2), regenerating the glutathione. This means GLO1 activity is directly dependent on glutathione availability — any process that depletes glutathione will impair methylglyoxal clearance.

1.6 The Polyol Pathway (AKR1B1)

AKR1B1 (aldo-keto reductase family 1 member B1, also called aldose reductase) is the rate-limiting enzyme of the polyol pathway, an alternative route for glucose metabolism. Under normal glucose concentrations, the polyol pathway handles a small fraction of glucose. However, the pathway becomes increasingly active as glucose rises because aldose reductase has a relatively high Km for glucose (~70 mM). The pathway converts glucose to sorbitol (consuming NADPH in the process), and sorbitol dehydrogenase then converts sorbitol to fructose.

This pathway contributes to glycation through three mechanisms. First, fructose is 7–10 times more reactive than glucose as a glycating agent and generates fructose-3-phosphate, which decomposes to 3-deoxyglucosone, another potent glycating compound. Second, the NADPH consumed by aldose reductase is the same cofactor needed by glutathione reductase to regenerate reduced glutathione (GSH) from its oxidized form (GSSG). This creates direct competition with the glyoxalase system: more polyol pathway activity means less NADPH available for glutathione regeneration, which means less glutathione available for GLO1 to detoxify methylglyoxal. Third, sorbitol accumulation increases intracellular osmotic pressure, which can affect cell membrane dynamics.

1.7 AGE Receptors (RAGE / AGER)

AGER (advanced glycation end product receptor, also called RAGE) is a pattern recognition receptor on cell surfaces that binds AGEs and triggers intracellular inflammatory signaling through NF-κB activation. While RAGE does not affect the glycation rate itself, it determines the biological consequences of glycation. When AGEs bind RAGE, they activate inflammatory cascades that promote oxidative stress, endothelial dysfunction, and vascular damage. RAGE exists in both membrane-bound form (pro-inflammatory) and soluble form (sRAGE, which acts as a decoy receptor and is anti-inflammatory). The balance between these forms, and the receptor's binding affinity, are influenced by genetic variants.