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Genetic Determinants of Variability in Glycated Hemoglobin (HbA_{1c}) in Humans: Review of Recent Progress and Prospects for Use in Diabetes Care

Nicole Soranzo

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Abstract Glycated hemoglobin A_{1c} (HbA_{1c}) indicates the percentage of total hemoglobin that is bound by glucose, produced from the nonenzymatic chemical modification by glucose of hemoglobin molecules carried in erythrocytes. HbA_{1c} represents a surrogate marker of average blood glucose concentration over the previous 8 to 12 weeks, or the average lifespan of the erythrocyte, and thus represents a more stable indicator of glycemic status compared with fasting glucose. HbA_{1c} levels are genetically determined, with heritability of 47% to 59%. Over the past few years, inroads into understanding genetic predisposition by glycemic and nonglycemic factors have been achieved through genome-wide analyses. Here I review current research aimed at discovering genetic determinants of HbA_{1c} levels, discussing insights into biologic factors influencing variability in the general and diabetic population, and across different ethnicities. Furthermore, I discuss briefly the relevance of findings for diabetes monitoring and diagnosis.

Keywords Glycated hemoglobin · HbA_{1c} · Genome-wide association study · Single nucleotide polymorphism · Genetic · Diabetes

Clinical Trial Acronyms

ARIC	Atherosclerosis Risk in Communities
DCCT	Diabetes Control and Complications Trial
GoKinD	Genetics of Kidneys in Diabetes
MAGIC	Meta-Analyses of Glucose and Insulin Related Traits Consortium

N. Soranzo (✉)
Human Genetics, Wellcome Trust Sanger Institute,
Genome Campus,
Hinxton CB10 1HH, UK
e-mail: nicole.soranzo@sanger.ac.uk

Introduction

Type 2 diabetes is a common metabolic disorder defined by the presence of markedly elevated levels of plasma glucose [1], which arise from dysregulations in the complex interplay between pancreatic β-cell function and insulin sensitivity in hepatic and skeletal muscle cells. Genetic association studies have recently revealed nearly 40 robustly replicated loci for type 2 diabetes [2]. Parallel, high-powered genome-wide analyses of quantitative glycemic traits [3–6, 7••] have provided alternative insights into the function of these loci, which are informing our understanding of disease pathophysiology.

Glycated hemoglobin A_{1c} (HbA_{1c}), or the percentage of total hemoglobin that is bound by glucose, provides a better estimate of average glycemia than routine determinations of blood glucose concentration, and is the most widely used index of chronic glycemia [8, 9]. It results from the nonenzymatic chemical modification of hemoglobin molecules carried in erythrocytes by glucose. The glycation process involves the nonenzymatic attachment of glucose to the NH-terminal N-terminal valine and internal lysine amino groups of hemoglobin [10]. The glycation reaction is mostly irreversible, so that the concentration of HbA_{1c} is a function of the concentration of glucose to which the erythrocytes are exposed over their lifespan (120 days on average). HbA_{1c} therefore represents a surrogate marker of average blood glucose concentration over the previous 8 to 12 weeks, thus representing a longer-term indicator of glycemic status compared with fasting glucose [11].

HbA_{1c} levels are better predictors than fasting glucose of the development of long-term complications in type 1 and type 2 diabetes [12], and higher levels in the subdiabetic range have been shown to predict type 2 diabetes risk and cardiovascular disease [13, 14]. For these reasons an

International Expert Committee has recently proposed a revision of the diagnostic criteria for diabetes, recommending that HbA_{1c} may be a better means of diagnosing diabetes than measures of glucose (fasting and/or post-challenge) and that it be adopted as a diagnostic criterion for diabetes [15].

The heritability of HbA_{1c} levels is relatively high (47% to 59%) when compared with fasting glucose (34% to 36%) or glucose level 2-hour post-oral glucose tolerance test (OGTT) (33%) [16, 17], and thus amenable to genetic analysis. Here I review current research aimed at discovering genetic determinants of HbA_{1c} levels, discussing insights into biologic factors influencing variability in the general and diabetic population, and across different ethnicities. Furthermore, I discuss the relevance of findings for diabetes monitoring and diagnosis.

The First Generation of Genetic Studies: Linkage Scans and Candidate Gene Association Studies

There is a relative paucity of published reports on linkage and candidate gene association studies for HbA_{1c} levels. The Framingham Heart Study conducted a genome-wide search for diabetes-related genes using measures of glycemia as quantitative traits (20-year mean fasting glucose, current fasting glucose, and HbA_{1c}). A total of 771 men and women from 330 pedigrees from the 5th Offspring Study exam cycle (1991–1995) had information on HbA_{1c} levels and were typed at 401 microsatellite markers (at an average spacing of 10 cM). Peak evidence for linkage to HbA_{1c} levels was on the long arm of chromosome 1 at 187 cM (multipoint logarithm of the odds score, 2.81), in a model accounting for age, cigarette smoking, alcohol and estrogen use, physical activity, and body mass index. The same broad chromosomal region had been reported as having evidence for linkage for type 2 diabetes and quantitative fasting traits.

Among the first candidate gene studies, Shima et al. [18] tested the association of variants in the calpain-10 gene (*CAPN10*) gene—a candidate gene for type 2 diabetes originally reported in Mexican Americans—with several metabolic traits in 286 unselected Japanese subjects. They found one single nucleotide polymorphism (SNP-19) associated with higher body mass index and HbA_{1c} levels at the nominal level under the dominant model (P=0.003 and P=0.024, respectively), indicating a contribution of *CAPN10* variants to mild obesity and glucose intolerance in Japanese. More recently, Krízová et al. [19] tested associations of variants at two candidate genes of insulin resistance and type 2 diabetes mellitus, adiponectin (*ADIPOQ*) and resistin (*RETN*), in individuals of European ancestry. They genotyped SNPs 45T>G and 276G>T in *ADIPOQ* and 62G>A and −180C>G in *RETN* in patients with obesity, anorexia nervosa, and in control healthy normal-weight women, and tested associations with serum concentrations of these hormones and measures of insulin sensitivity and metabolic traits, including tumor necrosis factor-α, insulin, cholesterol, HbA_{1c}, and blood glucose levels. They found significant associations of SNP ADP+276G>T allele with higher cholesterol levels in patients with anorexia, higher adiponectin concentrations in obese patients, and lower HbA_{1c} levels in normal women. SNP of the resistin gene 62G>A was associated with lower HbA_{1c} in normal women and higher cholesterol concentrations in the obese group. However, neither of these two associations at *CAPN10* and *RETN* was replicated in further, high-powered genome-wide association studies (GWAS).

Locus Discovery through GWAS in Healthy Individuals

The advent of genome-wide SNP arrays and imputation-based meta-analysis has provided a robust statistical framework for discovery and replication, and boosted locus discovery revealing a wealth of genetic loci associated with disease and quantitative end points. GWAS of fasting glucose levels led to the identification of associations with HbA_{1c} at three loci (*G6PC2*, *MTNR1B,* and *GCK*) [4, 5, 20–25]. The association of *MTNR1B* with HbA_{1c} was furthermore replicated in 3210 unrelated Chinese Hans from Beijing [26], whereas to date no GWAS have been reported in non-European samples.

In the first GWAS of HbA_{1c} levels, Paré et al. [27•] investigated 337,343 SNPs in 14,618 healthy women of European ancestry from the Women's Genome Health Study, and validated their findings in 455 nondiabetic Caucasian participants recruited from the Boston metropolitan area. They detected four loci with significant association at the genome-wide level of 10^{-6}. Of these, three were previously associated with type 2 diabetes or glycemic end points (*GCK*, *SLC30A8,* and *G6PC2*) [20, 21, 23, 25, 28] and in people free of diabetes. The fourth mapped to an intron in *HK1*, and was a novel locus.

Investigators of the MAGIC recently completed the largest to date meta-analysis of HbA_{1c} levels [7••]. The genome-wide discovery set used in this study included approximately 2.5 million genotyped and imputed autosomal SNPs genotyped in 35,920 participants, a sample size that has 80% power to detect SNPs explaining 0.12% of the trait variance at the genome-wide significant threshold of $P=5\times10^{-8}$. The analysis confirmed a strong statistical support at *GCK, G6PC2/ABCB11*, *MTNR1B*, and *HK1*, confirming previous reports [5, 21–25, 27•]. Furthermore, novel evidence for association was detected at six loci (in or near *FN3K*, *HFE, TMPRSS6, ATP11A/TUBGCP3*, *ANK1,* and *SPTA1)*.

In parallel, Franklin et al. [29] completed a GWAS meta-analysis of glycated hemoglobin levels in 1782 healthy individuals from three genetically isolated populations: the Orkney Isles in the north of Scotland, the Dalmatian islands of Vis, and Korčula in Croatia. They reported a genome-wide significant association at an intronic variant in the *TCF7L2* gene, the strongest common genetic risk factor for type 2 diabetes. An association at the same locus was also reported by Karns et al. [30] in a small sample of 843 individuals.

Associations with Correlated Metabolic and Hematologic Traits and Disease Provide Insights into Biologic Determinants of HbA_{1c} Variance

In addition to ambient glycemia, it is known that medical conditions that change erythrocyte turnover, hereditary anemias, and iron storage disorders can influence the variability of HbA_{1c} in populations [31]. The former include hemolytic anemias, chronic malaria, major blood loss, or blood transfusion; the latter are caused by rare causative mutations in genes involved in erythrocyte membrane stability, hemoglobin function, and glucose sensing and membrane transport in erythrocytes. It is thus of interest to assess if genetic variation segregating at high frequencies in the population, and causing subtler variation in these parameters, might also affect HbA_{1c}. Furthermore, it is important to establish whether variation due to nonglycemic factors affects the utility of HbA_{1c} in clinical practice.

Evidence from GWAS (Table 1) supports the notion that common variants might affect HbA_{1c} levels through their effects on glucose levels and also through erythrocyte biology. A first evidence for this came from the study of Paré et al. [27•], who identified associations at four loci, including *GCK*, *SLC30A8*, *G6PC2,* and *HK1*. *HK1* encodes the enzyme hexokinase, which catalyzed the first step in glycolysis and thus represents a likely candidate for the control of glucose metabolism. *HK1* is the only isoform that is essential for red blood cell glucose metabolism [32], and is the predominant form among the four isozymes of the hexokinase family (HK1, HK2, HK3, and glucokinase). It is expressed in the vast majority of cells and tissues, including cells that are strictly dependent on glucose uptake for their metabolic needs [33]. In humans, rare nonsynonymous substitutions in the active site of *HK1* and intragenic deletions have been shown to cause *HK1* enzymatic deficiency associated with autosomal-recessive severe non-spherocytic hemolytic anemia [33–36]. The downeast anemia mice display *HK1* deficiency and a similar anemic phenotype [32].

These observations led Bonnefond et al. [37•] to postulate that *HK1* genetic variation may indirectly alter HbA_{1c} measurements by generating a proanemic state, and independently of ambient blood glucose levels. They assessed the impact of the sentinel SNP at *HK1* on HbA_{1c}, glucose control-related traits (fasting- and 2-hour post-OGTT–related parameters), type 2 diabetes risk, and red blood cell–related parameters in Europeans. Surprisingly, the most associated SNP at this locus showed no association with any other markers of glucose control, whereas it was significantly associated with hemoglobin levels, hematocrit, and anemia.

The subsequent study by the MAGIC investigators [7••] provided additional evidence of HbA_{1c}-associated loci with no evidence for association with glucose-control traits. Of the 10 loci associated with HbA_{1c} at the genome-wide level, three had significant evidence for association of the HbA_{1c}-raising allele with fasting glucose and β-cell function (*GCK*, *MTNR1B*, and *G6PC2*) in this and previous studies, and *GCK* also with 2-hour glucose [3–6, 24, 25, 27•, 38, 39]. Two of them (*GCK* and *MTNR1B*) were also associated with type 2 diabetes [3]. For the remaining seven we found no evidence for association with glycemic traits and diabetes, nor with insulin levels, despite adequate power. Of these, associations at the *HFE* and *TMPRSS6* loci mapped to known functional variants in two complementary and directionally consistent pathways [40] and were associated with quantitative hematologic traits [7••, 41, 42]. At *HFE* the A allele at rs1800562 (Cys262Tyr), which is responsible for hereditary hemochromatosis (MIM 235200), was associated with lower levels of HbA_{1c}, rather than the higher levels one would predict from epidemiologic observations of the increased *HFE* mutation prevalence in patients with type 2 diabetes [43, 44]. The reciprocal observation was seen for *TMPRSS6*, where the A allele at SNP rs855791 (Val736Ala) was associated with lower hemoglobin levels and higher HbA_{1c} levels.

Three additional loci (*SPTA1*, *ANK1*, and including *HK1* discussed earlier) showed suggestive associations with erythrocyte indexes, and rare variants at these loci cause hereditary anemias [45, 46]. We postulated that functional variants at *HK1* may affect a potential dissociation between ambient plasma glucose and intracellular cytoplasmic glucose, and that the hemoglobin-lowering variant may affect the overall percent of HbA_{1c} through an increased glucose/hemoglobin molar ratio, which in turn could increase the rate of hemoglobin that is glycated at a given glucose level. We further postulated a possible role of erythrocyte membrane stability and altered erythrocyte lifespan (*ANK1*, *SPTA1*) and hemoglobin deglycation (*FN3K*) based on the known function of the respective gene products mapping to the vicinity of the association signals.

These patterns were confirmed in analyses conditioned on fasting glucose or hematologic traits, which provided statistical support for an effect on HbA_{1c} via regulation of

Table 1 Summary of genetic variants robustly associated with HbA_{1c} and correlated hematologic and metabolic traits in GWAS

Region	Locus	SNPs	PubMed	RAF	β (95% CI)[a]	*P*	Correlated trait association[b]
1q23.1	*SPTA1*	rs2779116	20858683	0.27	0.02 (0.01–0.03)% increase	3×10^{-9}	
2q31.1	*G6PC2/ABCB11*	rs1402837	19096518	0.23	0.02 (NR)% increase	5×10^{-10}	rs560887-FPG (18451265)
							rs560887-FPG (19060907)
		rs552976	20858683	0.64	0.05 (0.04–0.06)% increase	8×10^{-18}	rs563694-FPG (18521185)
							rs560887-HOMA-B (20081858)
6p22.2	*HFE*	rs1800562	20858683	0.94	0.06 (0.05–0.07)% increase	3×10^{-20}	rs1408272-MCH (19862010)
							rs198846-Hgb (19820698)
7p13	*GCK*	rs730497	19096518	0.17	0.03 (NR)% increase	6×10^{-12}	rs4607517-FPG (19060907)
		rs1799884	20858683	0.18	0.04 (0.03–0.05)% increase	1×10^{-20}	rs4607517-HOMA-B (20081858)
8p11.21	*ANK1*	rs6474359	20858683	0.97	0.06 (0.04–0.08)% increase	1×10^{-8}	
		rs4737009	20858683	0.24	0.03 (0.02–0.04)% increase	6×10^{-12}	
8q24.11	*SLC30A8*	rs13266634	19096518	0.3	0.02 (NR)% decrease	5×10^{-8}	rs13266634-T2D (17293876, 17460697, 17463246, 17463248, 17463249, 19056611, 19401414), FPG (19734900)
							rs3802177-T2D (20581827)
							rs11558471-FPG (20081858)
10q22.1	*HK1*	rs16926246	20858683	0.9	0.09 (0.08–0.10)% increase	3×10^{-54}	
		rs7072268	19096518	0.5	0.05 (NR)% increase	2×10^{-25}	
10q25.2	*TCF7L2*	rs7903146	20849430	0.72	0.05 (0.02–0.08)% HbA_{1c} decrease	1×10^{-7}	rs7901695-T2D (17463249)
							rs4506565-FPG (20081858)
							rs7903146-T2D (17293876, 17460697, 17463246, 17463248,17668382, 18372903, 19056611, 19401414, 19734900, 20581827)
							rs12243326-OGTT (20081857)
11q14.3	*MTNR1B*	rs1387153	20858683	0.28	0.03 (0.02–0.04)% increase	4×10^{-11}	rs1387153-T2D (20581827)
							rs1387153-FPG (19060909)
							rs2166706-FPG (19651812)
							rs10830963-HOMA-B (20081858), -FPG (19060907)
13q34	*ATP11A/TUBGCP3*	rs7998202	20858683	0.14	0.03 (0.02–0.04)% increase	5×10^{-9}	
17q25.3	*FN3K*	rs1046896	20858683	0.31	0.04 (0.03–0.05)% increase	2×10^{-26}	
22q12.3	*TMPRSS6*	rs855791	20858683	0.42	0.03 (0.02–0.04)% increase	3×10^{-14}	rs855791-Hgb (19820698)
							rs2413450-MCH (19862010)

Note that this table includes only results from GWAS studies, and intentionally omits candidate-SNP and candidate-gene studies

[a] Not reported

[b] rsID, associated trait, PubMed ID; values are given for associations from genome-wide scans

FPG fasting plasma glucose; *GWAS* genome-wide association studies; *HbA_{1c}* hemoglobin A_{1c}; *Hgb* hemoglobin; *HOMA* homeostatic model assessment; *MCH* mean corpuscular hemoglobin; *OGTT* oral glucose tolerance test; *RAF* risk allele frequency; *SNP* single nucleotide polymorphism; *T2D* type 2 diabetes

systemic glucose concentrations for *GCK, G6PC2,* and *MTNR1B*, and via hematologic parameters for *HFE*, *TMPRSS6,* and *HK1*. Taken together, these results suggest that these common variants influence HbA_{1c} levels via glycemic levels as well as erythrocyte physiology. Specific mechanisms are suggested by existing knowledge on the function of leading candidate genes in each region. These hypotheses will need to be tested to understand mechanistically and physiologically the effects of these genetic variants.

Discovery Studies in Individuals with Diabetes

The GWAS described before were all carried out in healthy individuals, using standardized analysis protocols and trait definition. The strength of this approach is that association results are not influenced by strong environmental confounders, principally disease status and antidiabetic medication. The observation that genetic associations underlying HbA_{1c} levels at some loci are independent from fasting glucose reflects earlier observations in a classical discordant

monozygotic (MZ) twin design by Snieder et al. [47]. Such analysis revealed a significant correlation in HbA_{1c} levels in 45 MZ twins discordant for the disease (r=0.52, P< 0.001; as opposed to r=0.68, P< 0.001 in 33 MZ twins concordant for diabetes), suggesting that a substantial proportion of heritability was due to diabetes-independent familial effects. Although robust estimates of the proportion of phenotypic variance attributable to diabetes-independent genetic effects are still lacking, these results showed for the first time that familial factors might explain variation in HbA_{1c} levels that is not dependent on glycemic control.

Recently, Paterson et al. [48•] carried out a genome-wide analysis on repeated measures of HbA_{1c} from the DCCT with the aim to identify genetic loci underlying glycemic control in individuals with type 1 diabetes. The study sample consisted of two sets of individuals sampled from the conventional (n=667) and intensive (n=637) treatment groups of the DCCT. Genome-wide SNPs were tested for association with mean HbA_{1c}, stratified by intervention arm as well as in the combined cohort. This analysis yielded a large number of SNPs (233) significant at the set threshold of $P=10^{-4}$, indicating an excess of false-positive owing to relatively underpowered study samples. Successive steps were used to prioritize loci for replication, assessing the association of these loci with capillary glucose and repeated measures of multiple complications of diabetes. For replication, associations were assessed through a series of (non-independent) analyses testing associations with quarterly HbA_{1c} using repeated measures, with mean daily glucose and baseline C-peptide (to confirm a glycemic mechanism), with HbA_{1c} repeated measures in the combined cohort (adjusting for treatment group and testing for interaction with treatment), and with glycemic complications including coronary calcium, neuropathy, hypoglycemia, and time to renal or retinal complications (in each arm separately).

Loci having evidence for association after these steps, including SNPs near *SORCS1* at 10q25.1, *GSC* at 14q32.13, *BNC2* at 9p22, and *WDR72* at 15q21.3, were carried forward for replication in two independent replication samples. These included the GoKinD study, a case–control collection of patients with type 1 diabetes with and without diabetic nephropathy, and healthy subjects from the MAGIC meta-analysis described earlier. These analyses revealed a locus (rs1358030 near *SORCS1*) where association reached the widely accepted threshold for genome-wide significance of $P<5\times10^{-8}$ in the conventional treatment group, which was also associated with mean glucose and showed suggestive evidence for replication in the intensive treatment group and in the control group in GoKinD. However, this association was not seen among GoKinD participants with nephropathy nor in the MAGIC sample. Another signal near *BNC2* showed suggestive evidence in MAGIC but did not replicate in GoKinD. SNPs in both regions were associated with diabetes complications in the expected direction: *SORCS1* with hypoglycemia (and less robustly with both retinopathy and nephropathy) and *BNC2* with microvascular end points.

It remains to be established if these variable replication outcomes stem from limited study power, or reflect the variable effect of the environment—most notably insulin treatment—in the two study arms of the study. We direct the readers to an accompanying editorial to the study [49] for a more detailed exploration of these effects. A recent study explored the same four loci *BNC2*, *SORCS1*, *GSC,* and *WDR72* for their effect on glycemic control in type 2 diabetes [50]. The authors typed 1486 subjects with type 2 diabetes from a Norwegian population-based cohort (HUNT2), and tested their effects on HbA_{1c} and non-fasting glucose levels individually and in a combined genetic score model. They detected no significant associations with HbA_{1c} or glucose and partially inconsistent direction of associations. Further studies in other populations are needed to identify whether genetic variants affect glycemic control in type 1 and type 2 diabetes.

Impact of Genetic Discoveries on the Use of HbA_{1c} in Diabetes Monitoring, Diagnosis, and Treatment in Europeans

Recently, an International Expert Committee has proposed a revision of the diagnostic criteria for diabetes, recommending that HbA_{1c} may be a better means of diagnosing diabetes than measures of glucose (fasting and/or postchallenge) and that it be adopted as a diagnostic criterion for diabetes [51]. The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the HbA_{1c} ≥48 mmol/L (≥6.5%) as another criterion for the diagnosis of diabetes [52]. The recommendation is based on the association of microvascular complications with HbA_{1c} being at least as strong as those with fasting or postchallenge glucose, that HbA_{1c} is subject to less day-to-day variability than fasting or postchallenge glucose, and that it can be measured at any time of the day without preparations such as fasting or a glucose challenge. It is likely that practical, medical, methodologic, and financial factors will prevent implementation of the recommendation in the majority of clinical settings. It is nevertheless important to understand how genetic factors underlying normal variation in HbA_{1c} through nonglycemic routes might influence diabetes diagnosis.

In addition to severe pathologies characterized by altered erythrocyte physiology (e.g., inherited hemoglobinopathies) that may influence the utility of HbA_{1c} in diabetes diagnosis [31, 51, 53, 54], we and others showed that genetically determined physiologic variation in the general population can also play a role, affecting HbA_{1c} levels through subtler but more widespread alterations of iron

levels and/or hemoglobin concentration. We sought to quantify these genetic effects in population-level terms, and to evaluate the resulting risk of misclassifying individuals as diabetic or nondiabetic owing to genetic influences on HbA_{1c}. Using net reclassification analysis, we estimated that the population-level impact of the seven nonglycemic loci when HbA_{1c} ≥6.5% is used as the reference cutoff for diabetes diagnosis was approximately 2% (P=0.002). This estimate represents an upper boundary for the effect of these common variants, as most people (the majority in the center of the distribution) are expected to have a smaller individual genotype effect size. This suggests that variation in HbA_{1c} levels due to common, nonglycemic effect variants might influence only minimally diagnosis or misclassification of diabetes.

Interethnic Differences in the Allelic Architecture of HbA_{1c} Levels and Their Impact on Diabetes Diagnosis

HbA_{1c} values are higher in African Americans than in the population of European ancestry. Furthermore, variants at loci controlling iron metabolism associated with HbA_{1c} levels are known to vary across ethnic groups. For instance, the A allele frequency at rs1800562 (*HFE*) is absent in populations of West African and East Asian ancestry (www.hapmap.org) but is relatively common (~5%) in Europe. The T allele at rs855791 (*TMPRSS6*) is at approximately 39% in Europeans, but relatively rare in West African (~11%) and East Asian (~5%) populations. These observations raise the question of how variation in frequency and effect size in diverse populations may affect reclassification of diabetes status by HbA_{1c}.

Although the effect of individual loci has not been explored, Maruthur et al. [55•] explored the contribution of inherited interethnic differences in HbA_{1c} levels in a cross-sectional analysis of 2294 individuals of African American ancestry from the community-based ARIC study. As rates of admixture with Europeans vary among African Americans, the percentage of European genetic ancestry for each individual, estimated from ancestry-informative markers, was compared with HbA_{1c} levels categorized using American Diabetes Association diagnostic cut points (<5.7, 5.7–6.4, and ≥6.5%). This analysis showed that HbA_{1c} levels were positively correlated to the fraction of the genome that was of European origin (P<0.001), although this correlation accounted for a minimal fraction (<1%) of the overall variability. Compared with genetic ancestry, socioeconomic, demographic, and metabolic risk factors were estimated to play a considerably greater role in governing changes in HbA_{1c}. As previously discussed for Europeans, these results suggest that the inherited variability among populations is likely to have a negligible impact on HbA_{1c}-based diabetes classification, and that the relative contribution of demographic and metabolic factors far outweighs the contribution of genetic ancestry to HbA_{1c} values in African Americans.

Conclusions and Outlook

Current evidence suggests that high-powered genetic analyses provide important new opportunities for dissecting genetic influences of HbA_{1c} levels. These initiatives will be important not only to better understand genetic and biologic determinants of HbA_{1c} variation in the general population, but also to inform recent initiatives to focus diabetes diagnosis and care more centrally on HbA_{1c}. It will be of considerable interest in the future to explore additional areas of study.

First, as more variants are discovered through sequencing and fine-mapping efforts, it will be important to reassess genetic predisposition and reclassification rates in European and non-European populations. Second, it will be important to extend the study of genetic influences to HbA_{1c} in prediabetic and diabetic populations, although the confounding effects of treatment might obscure any role of these polymorphisms in the diabetic population. Finally, additional genetic associations may be revealed from studies of low-to-intermediate frequency variants through imputation from the 1000 Genomes Project, direct association using whole-genome sequencing data, and in-depth replication and locus fine-mapping through custom arrays. These hypothesis-generating genetic efforts will pave the way for further studies of the role of the new loci in hemoglobin glycation, glucose metabolism, and diabetes.

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- •• Of major importance

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