Glucose homeostasis represents the outcome of a complex feedback system for maintaining glucose tolerance within rather narrow physiological limits. Aberrant glucose homeostasis contributes to a number of downstream effects, including insulin resistance. Insulin resistance occurs when muscle, fat, or liver does not appropriately use the insulin that is produced by the pancreas. As a result, more insulin is required to process the same amount of glucose, but with increasing insulin resistance, there are increasing levels of glucose in the circulation. Deviant glucose homeostasis, coupled with insulin resistance, results in both hyperglycemia and hyperinsulinemia, leading to risk of type 2 diabetes mellitus (T2DM) and the metabolic syndrome. Over the past 2 decades, the prevalence of insulin resistance, the metabolic syndrome, and T2DM has increased. Ethnic differences in T2DM and insulin resistance are evident, with nonwhite populations having the greatest risk. There continue to be significant gaps in our knowledge regarding the metabolic, behavioral, and genetic determinants of these conditions. Understanding the genetic basis of glucose homeostasis, insulin resistance, and T2DM should provide insight on known and novel metabolic pathways that identify potential therapeutic targets and mechanisms for intervention. (Arterioscler Thromb Vasc Biol. 2012;32:2091-2096.)

Key Words: insulin resistance ■ metabolic syndrome ■ diabetes mellitus ■ genetics ■ epidemiology

Glucose Homeostasis and the Metabolic Syndrome

Recent genome-wide association scans (GWAS) based upon assembly and meta-analyses of individual case–control and family-based designs have had an extraordinary impact on the development and expansion of the genetic basis of T2DM, glucose homeostasis (fasting plasma glucose and insulin), indirect measures of insulin resistance (homeostasis model assessment–insulin resistance [HOMA-IR]), and obesity (eg, body mass index [BMI]). More than 50 loci have been identified based upon analyses of single nucleotide polymorphisms (SNPs), with minor allele frequencies that are typically common (minor allele frequencies >0.05) in the populations under study with relatively small effect sizes. The strongest effect for T2DM is the rs7903146 SNP in the TCF7L2 gene with an odds ratio of ≈ 1.40; the strongest effect for obesity (BMI) is the rs9939609 SNP in the FTO gene with an odds ratio of ≈ 1.67. The meta-analyses of GWAS for T2DM, based upon the candidate genes in the loci identified, suggest that the primary pathways may involve the β-cell despite the recognition that insulin resistance is a major heritable
component of T2DM risk. Further, the SNPs identified as significantly associated with T2DM, glucose homeostasis, or obesity by GWAS, using a model of common genetic variation, does not account for a significant portion of the variation of these traits. These results suggest that other mechanisms, such as undetected common variants, infrequent/rare variants, structural variation, and gene–gene and gene–environment interaction, may be important. Finally, there has been recent evidence that genes identified for 1 phenotype (eg, BMI) may have pleiotropic effects on other phenotypes, such as glucose homeostasis and lipids. Thus, loci previously identified for lipids and other traits may, in fact, contribute significantly to the genetic risk for insulin resistance and T2DM.

### Direct and Indirect Measures of Glucose Homeostasis

Both decreased insulin sensitivity and secretion have long been known as characteristics of impaired glucose tolerance and T2DM. Subjects who are nondiabetic in high-risk populations for T2DM, such as Pima Indians and Hispanics, are hyperinsulinemic and insulin resistant; both hyperinsulinemia and insulin resistance predict the development of T2DM in many populations. Decreased insulin secretory capacity is a prominent aspect of established T2DM, and it has been difficult to establish insulin secretion as a precursor of T2DM. This difficulty is, in part, a result of the fact that measures of β-cell function need to take into account the increased insulin resistance found in prediabetic subjects. This concept has become known as the disposition index (DI). With the development of more sophisticated measurement techniques, decreased insulin secretion has been studied as an important predictor of T2DM in several cohorts. For example, small groups of Pima Indians who remained glucose tolerant over 3 clinic visits were compared with subjects who progressed to impaired glucose tolerance and then T2DM. Although both groups became more insulin resistant, the subjects who remained normal glucose tolerant were able to compensate by increasing their insulin secretion (as measured by the acute-phase insulin response [AIR]), whereas those who developed T2DM had an absolute decrease in AIR. Moreover, the magnitude of the insulin secretory defect appears to be magnified by adjusting for concomitant insulin resistance.

### Different Genetic Basis for Different Measures of Glucose Homeostasis?

It is clear that an individual's risk for developing T2DM (and measures of glucose homeostasis, obesity, and insulin resistance) is determined, in part, by genetic factors. The discovery of genes that account for variation in glucose homeostasis and the manner in which the β-cell responds could identify important pathways for insulin resistance, metabolic syndrome, and T2DM risk prediction, intervention, and treatment (Figure 1). Currently, the genetic basis of direct measures of glucose homeostasis is largely unknown. This lack of knowledge is in sharp contrast to the multitude of loci identified from GWAS for T2DM and indirect measures of glucose homeostasis, insulin sensitivity homeostasis model assessment-β cell (HOMA-B), and HOMA-IR.

Alterations in glucose homeostasis, mediated by genetic and nongenetic factors, are reflecting the body's metabolic control mechanisms. Despite moderate to high heritability, the genetic basis of the direct measures of insulin resistance and insulin secretion in European and non-European origin populations has not been clearly elucidated. A primary issue for understanding the genetic basis of glucose homeostasis is the phenotype. There are limited techniques for obtaining valid assessments of glucose homeostasis, as defined by insulin secretion or insulin resistance parameters, in either epidemiologic or clinical settings. HOMA-B has been applied as a simple measure of basal insulin secretion in many studies because it is based solely on fasting measures of glucose and insulin. In the frequently sampled intravenous glucose tolerance test (FSIGT), parameters are obtained from the glycemic response to endogenous and exogenous insulin, and the FSIGT provides measures of both insulin resistance and β-cell function. The magnitude of β-cell function impairment as estimated by HOMA-B is underestimated when compared with insulin.

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**Figure 1.** Genetic and epidemiological basis of glucose homeostasis, insulin resistance, and the metabolic syndrome.
secretion as estimated by AIR from the FSIGT or the proinsulin-to-insulin (P/I) ratio. These findings may partially reflect that HOMA-B only measures basal insulin secretion. The P/I ratio is a measure of proinsulin processing and may detect an earlier defect in β-cell function.

Heritability \( h^2 \), as estimated from family studies using variance components methods, provides a metric for the extent of familial aggregation (genetic contribution) in the variation of a quantitative trait. For indirect (fasting plasma glucose, insulin, HOMA-B, and HOMA-IR) and direct measures (insulin sensitivity [SI], AIR, and DI) the heritability estimates vary and suggest potentially different strength of genetic contribution. For example, a direct estimate of heritability for SI in the Insulin Resistance Atherosclerosis Study (IRAS) Family Study \( h^2=0.31 \) was significantly greater than that for HOMA-B \( h^2=0.16 \) or fasting insulin \( h^2=0.17 \). This estimate of heritability of SI is consistent with that found in Finland-United States Investigation of NIDDM Genetics (FUSION) \( h^2=0.28 \) and the HEAt, RIsk factors, exercise Training And GENetics (HERITAGE) Family Study \( h^2=0.32 \) in blacks, \( h^2=0.24 \) in whites. In the IRAS Family Study, the genetic correlation estimated between SI, fasting glucose, insulin, and HOMA-B was \( \approx 50\% \), suggesting that direct and indirect measures may not reflect the same physiological processes.

It should be recognized that estimates of heritability do not determine either the number of genes that account for variation in a trait, the identity of the genes, or the magnitude of their effect. As noted above, the candidate genes in loci that have been associated with T2DM have suggested that most may have their effect through the β-cell, and not through insulin resistance pathways. Nearly half of the nondiabetic, middle-aged adults in a multiethnic cohort are insulin resistant. If there are cases in the controls of T2D GWAS studies, then there may be variants that fail to be detected because of the phenotypic misclassification as the effect size would be reduced.

Recently, the number of cohorts contributing to consortia focused on T2DM genetics has increased and often includes those with additional phenotypes. These reports have provided increased power to detect loci contributing to indirect measures of glucose homeostasis. In a meta-analysis of 21 GWAS cohorts (Meta-Analyses of Glucose and Insulin-related traits Consortium [MAGIC]), robust statistical evidence for genome-wide association with fasting glucose was observed for SNPs in 8 loci (including the candidate genes ADCY5, FADS1, and GLIS3) and SNPs in 1 locus (with the candidate gene IGF1) with both fasting insulin and HOMA-IR. Importantly, SNPs in 5 loci associated with fasting glucose in nondiabetic individuals are also recognized as T2DM risk loci. Expanding upon MAGIC, a joint meta-analysis was conducted to determine whether genes involved in insulin resistance pathways (HOMA-IR) could be discovered by accounting for differences in obesity (BMI) and interactions between BMI and genetic variants. SNPs in 6 loci (including the candidate genes COBLL1/GRB14, IRS1, PPP1R3B, PDGFC, UHRF1/BP1, and LYPLAL1) were discovered that were associated with fasting insulin, high triglyceride and low high-density lipoprotein levels, suggesting a new series of pathways to identify genes with contributions to multiple phenotypes.

There are few studies that contain FSIGT-measured parameters of glucose homeostasis and, given the more invasive protocol to collect the phenotypic data, many of these studies are small and underpowered to detect genes with small-modest effects. A genome-wide linkage scan in the HERITAGE Family Study failed to identify SNPs with statistically significant results, although 3 regions (4q32.1, 9p11.2, and 10p15.3) were noted for follow-up. A GWAS in 229 IRAS Family Study Hispanic subjects represented an early attempt to discover genes involved in FSIGT-defined insulin sensitivity and resistance in nonwhite populations. SNPs with nominal association with SI, from the first-stage GWAS were genotyped in 1190 Hispanic subjects. The evidence of the association did not reach genome-wide significance. There were multiple SNPs, however, that exhibited suggestive evidence of association, including those in the candidate genes VIRP1 and MAGI1. MAGI1 (membrane-associated guanylate kinase, WW and PDZ domain containing 1; located on chromosome 3p14.1) is near the T2DM candidate gene ADAMTS9 that is part of a TCFL2-p53-p53INP1-dependent pathway that may be involved in liver and adipocyte insulin resistance.

**Genes and Risk Prediction**

A major theme of genetic studies is to provide evidence that specific variants in genes are not only associated with disease but also are predictive of disease. For complex phenotypes, such as glucose homeostasis, insulin resistance, and T2DM, the ability to identify those at risk and predict those in whom there will be decline in glucose homeostasis, increase in insulin resistance, and transition (short- or long-term) to T2DM is critical. This aspect of natural history of disease based upon genetic factors has not been well developed. As shown in Figure 2, the change in the acute insulin response to glucose (AIR\(_g\)) principally determines glucose tolerance status at follow-up; normal glucose tolerance is maintained by a compensatory increase in insulin secretion. Thus, failure to increase insulin secretion leads to impaired glucose tolerance, and a decrease in insulin secretion leads to overt T2DM. The 2-year change in insulin secretion (SI, measured by FSIGT) in Mexican Americans has been shown to be significantly heritable \( h^2=0.42, P=0.04 \), whereas change in percent body fat, fasting insulin, and fasting glucose levels (components of HOMA) was not heritable. Two reports from the prospective Botnia study show that subjects with a high genetic risk (based on multiple known T2DM risk alleles or on MTNR1B) do not increase their insulin secretion to compensate for the increase in insulin resistance as efficiently as do those with low genetic risk. These findings are particularly noteworthy as β-cell decline is a hallmark of T2DM and may represent a particularly unique phenotype. Recent data from MAGIC demonstrated that SNPs in 5 loci identified as affecting risk of T2DM also account for significant variation in fasting glucose levels in nondiabetic subjects. The magnitude of the effect on fasting glucose was not predictive of T2DM risk, suggesting that for these candidate genes, the mechanism by which fasting glucose is elevated leading to T2DM remains unknown.
Common and Infrequent/Rare Coding Variants

Previous genetic studies of T2DM, glucose homeostasis, insulin resistance, and obesity used GWAS approaches with catalogues of common variation. Recent advances in DNA sequencing have contributed to the discovery of rare, functional variants that have helped clarify the genetic architecture of a variety of common phenotypes. In particular, the use of sequencing coding regions of genes (exome sequencing) targets genomic variation of (potentially) functional significance. Exome sequencing in families with hypobetalipoproteinemia, frequently associated with mutations in \(APOB\), revealed rare coding variants in \(ANGPTL3\) and the identification of a novel role for \(ANGPTL3\) in the metabolism of low-density lipoprotein cholesterol.\(^{30}\) It remains unclear whether variants contributing to phenotypes have effects in the same or in different directions. For example, rare functional variants in several renal sodium handling genes were associated with blood pressure, and all of those variants tended to reduce the level of blood pressure.\(^{31}\)

Some rare variants in \(PCSK9\) cause an autosomal dominant form of familial hypercholesterolemia, whereas other rare variants are associated with low levels of low-density lipoprotein cholesterol and a reduced risk of coronary disease.\(^{32}\) Exome sequencing is only now being performed in large numbers of samples with respect to T2DM, glucose homeostasis, insulin resistance, and metabolic syndrome. The discovery of rare variants in combination with common variants will advance our understanding of biology of these phenotypes. For low-density lipoprotein cholesterol levels, there is little evidence that rare or infrequent variants account for the association identified by GWAS (common variants) (L.A. Lange, PhD, unpublished results, 2012). For low-density lipoprotein cholesterol, the exploration of coding region variation may provide a new collection of candidate genes and pathways for discovery. There are hints that rare variants in T2DM susceptibility genes have multiple effects but these studies require a highly integrative and multidisciplinary approach that incorporates cell biological and computational expertise to determine whether rare or common variants affect protein function.\(^{33}\)

Other Genetic and Epigenetic Mechanisms

It is likely that some trait-influencing SNPs will be in noncoding regions (introns or intergenic) that influence expression of genes; thus, the variants associated with glucose homeostasis will likely have complex molecular basis, and no single SNP will be clearly identified as the causal variant. Other mechanisms may also be important to explain the variation in glucose homeostasis, insulin resistance, and metabolic syndrome. Studies of \(Lin28a\) and \(Lin28b\) transgenic mice have shown them to be resistant to obesity and have enhanced glucose tolerance, suggesting that the \(Lin28/let-7\) pathway may play an important role in modulating glucose metabolism.\(^{34}\) Studies in animal models have provided important insights on potential mechanisms and pathways that can be tested in human populations.\(^{35}\) Other novel pathways may involve epigenetic mechanisms, such as DNA methylation and histone modification, interactions between host genes, environments, and the gut microbiome.\(^{36}\)

From Genes to Biology

As more information emerges on the genetic basis of glucose homeostasis, insulin resistance, and metabolic syndrome, functional analyses of genes and polymorphisms are critical to provide a better understanding of biology. Several resources will be required to support future functional studies. Lymphoblastoid cell lines or other primary cell lines from subjects would represent valuable resources for evaluation of gene expression profiles from genotypically defined individuals. Use of high-throughput siRNA knockdown experiments in \(\beta\)-cell, skeletal muscle, and liver cell models could be used to test the functional influence of genes on insulin secretion and insulin action. The identification of genes associated with measures of glucose homeostasis, insulin resistance, and metabolic syndrome sets the stage for combined studies of genetic, environmental, and physiological interactions which results in decline of \(\beta\)-cell function and development of T2DM and cardiovascular disease, each of which has a profound influence on human health.

Summary

The genetic basis of glucose homeostasis and its impact on insulin resistance and cardiovascular disease is complex. Studies of common variants (GWAS) have become more powerful because of the increased contribution of cohorts not only with T2DM cases and controls but with greater breadth of phenotypes. The large consortia have contributed greatly to our knowledge of genes that account for (relatively) small components of genetic risk for indirect measures of glucose
homeostasis (e.g., fasting glucose, fasting insulin, HOMA-B, and HOMA-IR). At the same time, the GWAS results have also confirmed the contribution of genes identified for other traits (lipids and obesity) to variation in glucose homeostasis, representing new physiological and interventional pathways. Direct measures of glucose homeostasis (either from the euglycemic clamp or FSIGT) may be closer to underlying biology, but the cost/labor involved in data acquisition has limited their use in large cohorts and application in genetic studies. There is much remaining to be learned about the genetic basis of glucose homeostasis and the relationship of genes to insulin resistance and T2DM. Exome sequencing holds the promise that novel genes that contain rare or low frequency coding variants will account for additional variation in glucose homeostasis. It is likely that variants (common and rare) will have different frequencies and functions whose impact will be associated with glucose homeostasis. Implementation of these and other genomic, transcriptomic, and metabolomics strategies will be required to increase our ability to identify genes and the biological basis of glucose homeostasis.

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