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The Emerging Genetic Architecture of Type 2 Diabetes

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Abstract

Type 2 diabetes is a genetically heterogeneous disease, with several relatively rare monogenic forms and a number of more common forms resulting from a complex interaction of genetic and environmental factors. Previous studies using a candidate gene approach, family linkage studies, and gene expression profiling uncovered a number of type 2 genes, but the genetic basis of common type 2 diabetes remained unknown. Recently, a new window has opened on defining potential type 2 diabetes genes through genome-wide SNP association studies of very large populations of individuals with diabetes. This review explores the pathway leading to discovery of these genetic effects, the impact of these genetic loci on diabetes risk, the potential mechanisms of action of the genes to alter glucose homeostasis, and the limitations of these studies in defining the role of genetics in this important disease.

We are in the midst of a worldwide epidemic of type 2 diabetes, obesity, and metabolic syndrome—each created by complex interactions between genes and environment. For decades, investigators have worked to unravel the role of genetics in type 2 diabetes through epidemiological studies, studies of candidate genes, and genetic linkage in families. While this has provided important insights into some rare monogenic forms of diabetes, understanding the genetics of common type 2 diabetes remains a major challenge. Over the past year, a number of exciting articles have been published based on high-throughput genome-wide association (GWA) studies. These have not only uncovered a number of new genetic loci associated with diabetes and provided new targets for mechanistic investigation, but are also forcing us to reconsider the degree of genetic heterogeneity and possibly even the role of genetics itself in the pathogenesis of type 2 diabetes. In this Review, we reconstruct the events that led to this major paradigm shift, review the findings emerging from these studies, and discuss the potential implications and limitations of these discoveries for understanding the basic pathophysiology, as well as prediction, prevention, and treatment of type 2 diabetes.

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SUPPLEMENTAL DATA

Supplemental Data include one table and can be found online at http://www.cellmetabolism.org/cgi/content/full/8/3/186/DC1/.

Type 2 Diabetes: A Major Public Health Problem Arising from Environmental and Genetic Exposures

More than 20 million Americans and over 170 million individuals worldwide suffer from diabetes mellitus (Hogan et al., 2003). Despite advances in treatment, diabetes is the leading cause of chronic renal failure, adult blindness, and limb amputation, and a major risk factor for heart disease, stroke, and birth defects (Krolewski and Warram, 2005). As a result, the cost of diabetes care in the U.S. currently exceeds $200 billion annually, representing over 12% of all health-care dollars. These staggering human and economic costs will increase further as the prevalence of diabetes is expected to double worldwide by 2025 (Cowie et al., 2006).

By far, the largest proportion of this public health problem derives from type 2 diabetes, which accounts for more than 90% of diabetes in the US and worldwide (Skyler and Oddo, 2002). Unlike type 1 diabetes, which is caused by insulin deficiency due to autoimmune destruction of pancreatic β cells, type 2 diabetes arises from an impairment in the ability of muscle, fat, and liver to respond to insulin, i.e., insulin resistance, combined with an inability of the β cell to respond normally to glucose by appropriately increasing insulin secretion (Kahn, 1994). While the relative contribution of these two defects to diabetes pathogenesis continues to be debated, longitudinal studies in high-risk individuals suggest that insulin resistance is an early phenomenon, occurring years before any evidence of glucose intolerance, whereas the β cell failure develops later in the pathogenesis of disease (Martin et al., 1992). On the other hand, other studies have shown that the disposition index, reflecting both insulin sensitivity and insulin secretion, is an early marker of and predictor of type 2 diabetes (Lyssenko et al., 2005; Bergman, 2007).

Both insulin resistance and β cell failure are thought to result from the complex interplay of many different pathways under the combined control of environmental and genetic factors (Figure 1). The role of genetics in type 2 diabetes (T2D) is indicated by the familial clustering of insulin sensitivity and insulin secretion, the higher concordance rate of T2D in monozygotic versus dizygotic twins, and the high prevalence of type 2 diabetes in certain ethnic groups (e.g., Pima Indians or Mexican Americans) (Weijnen et al., 2002; Flegal et al., 1991). It has been estimated that 30%–70% of T2D risk can be attributed to genetics (Poulsen et al., 1999). Patterns of inheritance suggest that type 2 diabetes is both polygenic and heterogeneous—i.e., multiple genes are involved and different combinations of genes play a role in different subsets of individuals. Exactly how many genes and what their relative contributions are, however, remains uncertain, with some investigators postulating that type 2 diabetes consists of two or three major types with some minor types (Rich, 1990; Kahn et al., 1996).

The Search for Type 2 Diabetes Genes in the Pre-Genome-wide Association (GWA) Era

Over the past two decades four approaches have been used to unravel the genetics of type 2 diabetes, each with some success (Table 1). The first approach was to focus on forms of type

2 diabetes transmitted with a Mendelian dominant pattern of inheritance and/or other specific clinical features. This led to the discovery of genes involved in maturity onset diabetes of the young (MODY); the genes involved in several syndromes of severe insulin resistance (the type A syndrome, leprechaunism, Rabson-Mendenhall syndrome, and lipoatrophic diabetes); the genes involved in neonatal diabetes; and the genes involved in mitochondrial diabetes and other rare genetic syndromes (Table 2). Together, these monogenic forms of type 2 diabetes account for less than 2%–5% of this disease. Defining these relatively rare diabetes genes, however, has provided novel insights into pathways involved in the regulation of glucose homeostasis. For instance, elucidating the family of MODY genes has highlighted a complex hierarchical network of transcription factors modulating β cell development and function (Duncan et al., 1998). Similarly, the discovery of mutations in the insulin receptor, Akt2, and PPARγ in syndromes of severe insulin resistance confirms the important role of these signaling proteins in vivo in humans (O'Rahilly, 2007). From a therapeutic perspective, the identification of mutations in the ATP-sensitive potassium channel (Kir6.2/*KCNJ11*) in infants with neonatal diabetes has been very important, allowing these children to be treated with oral sulfonylureas rather than lifelong insulin injections (Gloyn et al., 2004; Pearson et al., 2006). More interesting from a mechanistic perspective has been the discovery of mutations in genes not previously linked to diabetes, such as the genes for the nuclear membrane protein lamin A or the protein seipin (*BSCL2*) in certain forms of lipodystrophy and insulin resistance (Shackleton et al., 2000; Magre et al., 2001). However, exactly how mutations in these genes result in either lipodystrophy or severe insulin resistance remains unclear.

The second approach to identify diabetes genes has been to search for genetic variants in candidate genes that might be associated, i.e., more frequent, in individuals with common type 2 diabetes (Hansen and Pedersen, 2005). In general, these studies have focused on *functional candidate genes*—i.e., genes whose products are known to play a role in glucose homeostasis, or *positional candidate genes*—i.e., genes located in chromosomal regions that had been identified in linkage studies. By focusing on genes already implicated in glucose homeostasis, the functional candidate gene approach is geared toward confirming the role of genes in diabetes rather than discovering as-yet-unknown disease pathways. The positional candidate gene strategy has more potential for discovery of new genes; however, this approach is limited by the low sensitivity of linkage studies for multifactorial disorders and the large size of linked genetic intervals.

Despite these shortcomings, these approaches have had some success. Candidate gene studies led to the identification of a common amino acid substitution in the nuclear receptor and adipogenic transcription factor PPARγ (Pro12Ala, rs1801282), which has a modest, yet extensively replicated effect on the risk of type 2 diabetes (Beamer et al., 1998). Similarly, the diabetes-associated Glu23Lys variant was identified in the *KCNJ11* gene, which encodes Kir6.2, one of the two components of the K_{ATP} channel essential for normal glucose-stimulated insulin secretion (Barroso et al., 2003). Functionally significant polymorphisms have also been identified in proteins involved in insulin action, including a "gain-of-function" polymorphism (K121Q) in the insulin action inhibitor *ENPP1* (Pizzuti et al., 1999), the insulin receptor substrates IRS1 and IRS2 and phosphatidylinositol 3-kinase

(Almind et al., 1996; Almind et al., 2002). Some, but not all, of these associations with T2 DM have been confirmed by meta-analysis or studies in large, diverse populations (McAteer et al., 2008; Florez et al., 2004a). Positional candidate efforts, on the other hand, have been mostly inconclusive, despite identification of multiple genomic regions linked to diabetes (e.g., 1q, 20q) (Stern, 2002). One notable exception is the identification of *TCF7L2* as a type 2 diabetes gene (discussed below) (Grant et al., 2006).

A number of recent efforts have used microarray gene expression analysis in attempt to define genetic alterations in type 2 diabetes. These have uncovered two important findings. One is a defect in skeletal muscle of humans with T2D characterized by a coordinated decrease in the expression of nuclear-encoded genes involved in mitochondrial oxidative phosphorylation (Patti et al., 2003; Mootha et al., 2003). This appears to be secondary to reduced expression of the transcriptional coactivators PGC-1α and PGC-1β. Similar changes in expression have been observed in some cohorts of first-degree relatives of diabetic individuals, suggesting that these may be heritable traits (Patti et al., 2003), but thus far no primary genetic defect has been linked to these changes. Although polymorphisms in PGC-1 and epigenetic modification of complex subunits may contribute to age-associated reductions in expression (Ling et al., 2004, 2007, Ronn et al., 2008), other studies have suggested that this expression phenotype may be secondary, at least to some extent, to poor physical fitness, obesity, intramyocellular lipid accumulation, or insulin resistance itself (Crunkhorn et al., 2007). Furthermore, the role of these changes in diabetes pathogenesis is uncertain, since an animal model with primary reduced mitochondrial oxidative phosphorylation in muscle shows increased, rather than decreased, insulin sensitivity (Pospisilik et al., 2007).

A second potential type 2 gene was discovered via microarray analysis is the transcription factor ARNT/Hif1β. This was identified using islets isolated from humans with type 2 diabetes and was associated with altered expression of many other genes in the β cell involved in glucose sensing, insulin signaling, and transcriptional control (Gunton et al., 2005). Again, however, it is not clear which, if any, of these changes represent primary defects or are secondary to *trans*-acting genes or metabolic/environmental factors.

The GWA Revolution

By 2006 it had become clear that identifying the major genes of type 2 diabetes would require a paradigm shift. Such a shift was made possible by several parallel developments. One was the completion of the HapMap project aimed at characterizing the genome-wide pattern of linkage disequilibrium (Frazer et al., 2007). Linkage disequilibrium (LD) is a statistical association between alleles at separate but linked loci, usually resulting from a particular ancestral haplotype being common in the population studied (Strachan and Read, 2003). This phenomenon causes adjacent polymorphisms to be correlated to the point of being strong proxies for each other. With linkage disequilibrium, therefore, it becomes possible to select a set of 300,000 to 1 million single nucleotide polymorphisms (SNPs) that can represent most of the 10 million common SNPs estimated to be present in the human genome. Coupled with improved microarray technology allowing precise typing of a large

number of polymorphisms and access to DNA from large cohorts of patients with diabetes, the possibility of large GWA studies of diabetes became a reality.

It is important to keep in mind that the GWA approach is not without its own limitations. First, in its current implementation, it assumes that the genetic variants conferring susceptibility to type 2 diabetes are common, i.e., have a frequency of ≥5% in the population. While theoretical models support this assumption, rare variants have been shown to contribute significantly to the modulation of complex metabolic traits (Brunham et al., 2006). Second, the GWA strategy poses significant challenges in terms of study design and data interpretation. For example, type 2 diabetes is an age-dependent disease, and, thus any population of controls will include many individuals who might later develop diabetes. Third, given the hundreds of thousands of comparisons performed in the analysis, a large number of polymorphisms can be significant at the $p < 0.05$ or $p < 0.001$ level by chance alone. Thus, a much more stringent significance threshold must be used (e.g., $p < 2 \times 10^{-7}$ for a 300K array), meaning that a very large sample size is needed in order to preserve power. This, in turn, creates a financial challenge. The final, and perhaps most important, challenge is what to study. Type 2 diabetes is not only polygenic and heterogeneous, but also is closely linked to other metabolic phenotypes and has a progressive pathogenesis, starting with insulin resistance and β cell dysfunction progressing to clinical hyperglycemia (Figure 1). Since there are no precise markers for defining stages in this progress, GWA studies were forced to focus on cases with clinically defined type 2 diabetes, adding elements of complexity to interpretation of results.

The GWA Studies for Type 2 Diabetes Genes

By the late spring of 2007, the results of five independent GWA screens for type 2 diabetes genes had been published (Sladek et al., 2007; Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007; Steinthorsdottir et al., 2007) (see Table S1 for characteristics of each study), and these were followed by five smaller GWA studies (Salonen et al., 2007; Rampersaud et al., 2007; Hayes et al., 2007; Florez et al., 2007; Hanson et al., 2007). The five large studies were all conducted using a two-stage strategy consisting of a GWA screen in an initial cohort of unrelated cases and controls followed by replication of the most significant findings in additional sets. The screening and replication sets consisted primarily of European Whites, with the exception of the Decode study, which included groups of Chinese from Hong Kong and West Africans (Table S1). Altogether, the screening sets included more than 7,000 cases and 12,000 controls; the replication sets consisted of about 20,000 cases and 26,000 controls. The screening set of the McGill/Imperial College study stands out from others for the relatively young age at diagnosis (average ~45 years) and the low BMI (average 25.8) of the individuals with diabetes, a focus hoping to increase the probability of detecting genetic effects, while excluding genes related to the etiology of obesity. In the other four large studies, the phenotype of cases was closer to that of common type 2 diabetes, with average age at diagnosis in the sixth decade. In the DGI study, a large proportion of controls were matched to cases by BMI, whereas in the other studies, the BMI was lower in controls than cases by two or three points, similar to what is observed in the corresponding source populations. The GWA screens were based on the Illumina 300K or

Affymetrix 500K genotyping array, both capturing about 80% of common variants present in the human genome of Caucasian individuals.

While each GWA screen identified dozens of potential candidates, at least 15 loci emerged as being most consistently associated with risk of type 2 diabetes across multiple studies (Table 3). Three of these correspond to genes that had already been implicated in type 2 diabetes (*TCF7L2*, *KCNJ11*, *PPARG*); the other 12 represent new potential type 2 diabetes genes. Given the large number of cases and controls, these associations are highly significant. However, these large p values should not be confused with the magnitude of the genetic effect as quantified by its odds ratio (OR), which in all cases is relatively small (Table 3). Two other striking features of these studies were that most of the genes identified would not be considered typical candidate genes for type 2 diabetes, and in most cases the variants associated with type 2 diabetes were in noncoding regions of the gene, suggesting alterations in regulatory elements and gene expression rather than amino acid sequence. The following is a brief summary of the evidence linking these 15 loci to type 2 diabetes and some thoughts about possible mechanisms involved in their effects.

TCF7L2 (10q25)

The strongest association in all of the studies is with a region on chromosome 10q25 located in a 92 kb linkage disequilibrium (LD) block in the *TCF7L2* gene. While the identification of this type 2 diabetes locus predates the GWA era (Grant et al., 2006), the association of the *TCF7L2* locus with T2D is by far the strongest and most consistent signal across the GWA studies. In a meta-analysis of the WTCCC, Fusion, and DGI studies, the combined odds ratio of type 2 diabetes per copy of the “high-risk” allele is 1.37 (95% confidence interval, 1.31–1.43), with a combined p value of 10^{-48} (Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007). Individuals homozygous for the high-risk allele have about a doubling of diabetes risk, or to put it another way, about ~12% of them will have type 2 diabetes versus ~9% of heterozygotes and ~6% of noncarriers. The predisposing effect seems to be more pronounced among lean than obese individuals (Cauchi et al., 2008a; Watanabe et al., 2007).

TCF7L2, also known as TCF-4 or β-catenin interacting protein, is a high-mobility group box-containing transcription factor that is involved in the WNT signaling pathway, acting as a nuclear receptor for β-catenin (Yi et al., 2005; Prunier et al., 2004). Wnt signaling is critical for cell proliferation and involved in many aspects of embryogenesis, including adipogenesis (Prestwich and MacDougald, 2007), myogenesis (Cossu and Borello, 1999), and pancreatic islet development (McLin et al., 2007). TCF7L2 activation induces a variety of genes, including those for intestinal proglucagon and glucagon-like peptides-1 and -2 (Fehmann et al., 1995). The association with type 2 diabetes involves a common haplotype spanning part of intron 3, exon 4, and part of intron 4, but does not include any coding variants, suggesting an effect on gene expression as the most likely explanation for association with type 2 diabetes.

Clinically, carriers of the high-risk *TCF7L2* genotype have reduced insulin secretion (Florez et al., 2006a), suggesting a possible role for TCF7L2 in the β cell dysfunction of type 2 diabetes. Overexpression studies in β cells, however, have given conflicting results, in one

case showing a blunting of glucose-stimulated insulin secretion (Lyssenko et al., 2007) and in another a beneficial effect to protect islets from glucose- and cytokine-induced apoptosis and impaired function (Shu et al., 2008). Other studies suggest roles for TCF7L2 in T2D via control of the incretin axis, hepatic glucose production, and adipocyte function (Lyssenko et al., 2007; Cauchi et al., 2006). Actual expression data for TCF7L2 in humans are limited. One report indicates that islets from carriers of the risk genotypes have increased TCF7L2 mRNA compared to noncarriers (Lyssenko et al., 2007), but no significant difference in TCF7L2 expression was observed in islets or muscle in a study of unselected human T2D in the Diabetes Genome Anatomy Project (DGAP) (http://www.diabetesgenome.org) (Figure 2, bottom). TCF7L2 could exert its effect in a variety of ways, since TCF7L2 is expressed at high levels in a wide variety of tissues, including the hypothalamus (Figure 2, top).

SLC30A8 (8q24)

The next strongest SNP after those in *TCF7L2* is in a 33kb LD block within the coding region of *SLC30A8*, a zinc membrane transporter (Zn-T8) that is highly expressed in pancreatic islets (Figure 3, top) (Chimienti et al., 2004). This gene first emerged as a type 2 diabetes locus in the McGill/Imperial study (Sladek et al., 2007). Although this polymorphism ranked only 34th in the screening GWA set with ORs of 1.18 and 1.53 for heterozygotes and homozygotes, respectively, this was one of only a handful of SNPs for which the association with type 2 diabetes was confirmed in the replication sets. Replication was also obtained in the Decode, WTCCC, Fusion, and DGI studies (Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007; Steinthorsdottir et al., 2007).

Of all of the new potential type 2 diabetes genes, *SLC30A8* is one of the few involving a nonsynonymous polymorphism—an arginine to tryptophan substitution at amino acid 325 (Sladek et al., 2007). SLC30A8-overexpressing cells display enhanced glucose-stimulated insulin secretion (Chimienti et al., 2006), suggesting that the risk allele might act by impairing transporter function, thereby decreasing the amount of zinc available for cocrystallization with insulin in the secretory vesicles of β cells. Reduced pancreatic and islet zinc levels have been observed in some animal models of type 2 diabetes (Taylor, 2005), and zinc supplementation has been shown to improve glucose tolerance in db/db mice (Simon and Taylor, 2001). On the other hand, studies have not identified any deficiency of pancreatic zinc content in patients with type 2 diabetes (Taylor, 2005), and at least one study suggests that dietary zinc supplementation in humans with diabetes further decreased glucose tolerance (Raz et al., 1989). Since zinc has many roles in the cell in addition to its role in insulin crystallization, and since Zn-T8 is only one member of a large family of zinc transporters, more mechanistic studies are clearly warranted. SLC30A8 has also recently been identified as an autoantigen in human type 1 diabetes (Wenzlau et al., 2007).

HHEX/IDE/KIF11 (10q23)

A locus on 10q23 ranked third for association with T2D (after *TCF7L2* and *SLC30A8*) in the McGill scan, and was independently replicated in the WTCCC, Fusion, and DGI studies giving a small p value ($p = 5.7 \times 10^{-10}$), but a combined OR of only 1.13. SNPs at this locus have been also found to be associated with measures of insulin secretion in a large

multicentric study from Europe and in the DPP study (Pascoe et al., 2007; Moore et al., 2008). The association signal lies in a 295 Kb block of LD that includes at least three potential type 2 diabetes genes: *HHEX* (a homeobox transcription factor), *KIF11* (a kinesin interacting factor), and *IDE* (insulin degrading enzyme) genes (Table 3). Which, if any, of these genes actually contribute to type 2 diabetes risk is not known. Each of these genes shows rather broad tissue expression (Figure 2, top). Based on its provocative name and data suggesting roles in both insulin signaling and islet function (Farris et al., 2003), *IDE* would probably be viewed as the strongest biological candidate gene at this locus. However, a previous large study of *IDE* as a candidate for type 2 diabetes was negative (Florez et al., 2006b). Reanalysis of the DGAP data reveals no difference in expression of *IDE* in islets between the individuals with diabetes and healthy controls (Figure 2, bottom), while in muscle, expression of *IDE* is modestly reduced in T2 DM (21% decrease, $p = 0.05$). Despite its name, IDE is not an insulin-specific protease and has been shown to play roles in degradation of glucagon, brain amyloid proteins, and viral glycoproteins (Qiu et al., 1998). HHEX, on the other hand, is a transcriptional repressor, active in cardiac and pancreas development (Tanaka et al., 1999; Foley and Mercola, 2005), as well as WNT signaling (McLin et al., 2007), while KIF11 is involved in centrosome migration and mitosis (Kapitein et al., 2005).

CDKAL1 (6p22)

An association signal at 6p22 maps to a 15 kb linkage disequilibrium block in intron 5 of the gene for *CDKAL1* (CDK5 regulatory subunit-associated protein 1-like 1). The strongest association of 6p22 with T2D was observed in the Decode study (OR = 1.20) (Steinthorsdottir et al., 2007), with weaker association in the WTCCC, Fusion, and DGI study (combined OR = 1.12), and no association in the McGill/Imperial study (Sladek et al., 2007; Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007).

The *CDKAL1* gene encodes a 65 kD protein that is expressed in a broad range of tissues (Figure 2, top) and is believed to be an inhibitor of CDK5 (cyclin-dependent kinase 5). CDK5 itself has been shown to blunt insulin secretion in response to glucose and to play a permissive role in the decrease of insulin gene expression that results from glucotoxicity (Ubeda et al., 2006). Thus, one can speculate that reduced expression of *CDKAL1* would result in enhanced activity of CDK5 in β cells, and this would lead to decreased insulin secretion; in agreement, this locus was significantly associated with small decreases in insulin response to a glucose load (Steinthorsdottir et al., 2007; Saxena et al., 2007; Pascoe et al., 2007; Palmer et al., 2008, Stancáková et al., 2008). However, in the analysis of human islet and muscle expression data from DGAP, there does not appear to be a significant difference in the level of expression of *CDKAL1* between subjects with diabetes and controls (Figure 2, bottom).

CDKN2A/2B (9p21)

Two signals of association with T2D have been localized to chromosome 9p21. The first one —represented by SNP rs10811661—is supported by the DGI, WTCCC, and Fusion scans with a combined OR of 1.20 and a $p = 7.8 \times 10^{-15}$ (Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007). A second weaker signal in this region was detected by the WTCCC and

Fusion studies about 100 kb in a telomeric direction (SNP rs564398, $p = 1.3 \times 10^{-6}$ and $p = 0.039$, respectively). The two association signals, involving noncoding polymorphisms, are separated by a recombination hotspot and thus could be independent. The centromeric signal (SNP rs10811661) is close to the *CDKN2A* and *CDKN2B* genes (cyclin-dependent kinase inhibitor 2a and 2b) and the telomeric signal includes both of these genes. Both genes code for inhibitors of CDK4 (cyclin-dependent kinase 4). *CDKN2A* encodes two molecules, $p16^{INK4a}$ and p14 (ARF), while *CDKN2B* encodes $p15^{INK4b}$ (Kamb et al., 1994; Pomerantz et al., 1998).

CDK4 is involved in cell-cycle regulation in a wide variety of cells. Interestingly, mice with targeted disruption of this gene have small islets and develop insulin-deficient diabetes, while mice expressing a CDK4 form insensitive to physiological inhibitors exhibit β cell hyperplasia (Rane et al., 1999). However, a study of 1276 healthy individuals failed to observe any association between *CDKN2A* or *CDKN2B* polymorphisms and insulin secretion (Pascoe et al., 2007). These two genes, however, are widely expressed and could have effects in many other tissues (Figure 2, top). Furthermore, this region includes other genes, including a mitochondrial RNA processing endoribonuclease and the gene for methylthioadenosine phosphorylase (Nobori et al., 1996), as well as several ESTs. Interestingly, a “major” locus for coronary artery disease, abdominal aneurysms, and peripheral vascular disease has also been identified in this region (Helgadottir et al., 2007; McPherson et al., 2007, Helgadottir et al., 2008), suggesting a common genetic link between diabetes and vascular disorders (Stern, 1995).

IGF2BP2 (3q27)

Association signals at 3q27 were observed in the WTCCC, Fusion, and DGI scans, although the combined OR is only 1.14 ($p = 8.9 \times 10^{-16}$) (Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007). This is consistent with previous studies showing linkage at this location with quantitative metabolic traits and type 2 diabetes (Kissebah et al., 2000; Vionnet et al., 2000). The SNPs displaying the strongest association with type 2 diabetes lie in a 50 kb region within intron 2 in the gene coding for IGF-2BP2. IGF-2BP2 is not an IGF binding protein, but a protein that binds to the 5′UTR of the insulin-like growth factor 2 (IGF-2) mRNA, thereby regulating its translation (Nielsen et al., 1999). Several other genes with important metabolic functions are also within the radius of a potentially regulatory effect by the risk variants, including *PPP1R2* (protein phosphatase 1, regulatory subunit 2), *MAP3K13* (mitogen-activated protein kinase kinase kinase), *LIPH* (lipase H), *DGKG* (diacylglycerol kinase gamma 1), *AHSG* (alpha-2-HS-glycoprotein, a putative inhibitor of insulin receptor signaling), and *ADIPOQ*, the insulin-sensitizing adipokine adiponectin. Reanalysis of the DGAP human islet and muscle data shows no difference in expression of *IGF2BP2* in diabetes (Figure 2A), so whether the association with type 2 diabetes is mediated by an effect on the expression of *IGF2BP2* or these other genes will have to be addressed by further studies.

FTO (16q12)

In the WTCCC scan, the association signal at this locus (OR = 1.27, $p = 7.3 \times 10^{-14}$) was second in magnitude only to that of *TCF7L2* (Zeggini et al., 2007). The diabetes-associated

alleles at this location, however, were also strongly associated with increased BMI, and the association with type 2 diabetes was lost when the analysis was adjusted for body weight, suggesting that the effect on T2D risk is mediated by an effect on adiposity. Indeed, this locus has been associated with obesity, with ORs ranging from 1.3 to 1.9 (Frayling et al., 2007; Dina et al., 2007). Adults homozygous for the *FTO* risk allele weigh about 3 kg more than individuals not carrying this allele. About 16% of white Europeans are homozygous for the high-risk A allele, and these individuals are 1.7 times more likely to be obese than those homozygous for the low-risk T allele. The SNPs showing the strongest association lie in a 47 kb linkage disequilibrium block encompassing parts of the first two introns and exon 2 of the *FTO* gene.

The function of the *FTO* (fat and obesity associated) gene is still unclear. FTO shares sequence motifs with Fe(II)- and 2-oxo-glutarate-dependent oxygenases and is localized in the nucleus, where it catalyzes the demethylation of 3-methylthymine in single-stranded DNA (Gerken et al., 2007). In mice FTO mRNA is most abundant in the brain, particularly in hypothalamic nuclei governing energy balance (Figure 2, top). FTO levels in the arcuate nucleus are regulated by feeding and fasting (Gerken et al., 2007). Other genes in close proximity to the *FTO* polymorphism include an Akt interacting protein (AKTIP), two members of the ATP binding cassette subfamily C *(ABCC)*, and *KIAA1005/RPGRIP1L* (a gene of unknown function). Functional studies based on knockout and overexpression models will be needed to understand the pathways through which variants at this locus control body weight and glucose homeostasis.

KCNJ11 and PPARγ

Most of the genes previously identified through the candidate gene approach did not rank high for association with T2D in the GWA studies. *KCNJ11* and *PPARG* are two exceptions. Both were found to be associated with type 2 diabetes in the WTCCC, Fusion, and DGI studies with a combined OR of 1.14 ($p = 6.7 \times 10^{-11}$ and $p = 1.7 \times 10^{-6}$, respectively) (Zeggini et al., 2007; Scott et al., 2007; Saxena et al., 2007), and both involve nonsynonymous polymorphisms. The association with the KCNJ11 gene concerns a common glutamate to lysine substitution at position 23 (E23K). The lysine allele has been shown to reduce the sensitivity of β cell ATP-sensitive K^+ channels toward inhibitory ATP^{4-}, thereby increasing the threshold for insulin release (Schwanstecher et al., 2002). Consistent with this, this polymorphism has been associated with an insulin secretion defect in multiple studies (Nielsen et al., 2003, Florez et al., 2004b). However, the β cell may not be the only important target organ for *KCNJ11*. A transgenic mouse expressing a mutant Kir6.2 subunit (encoded by the *KCNJ11* gene) in the hypothalamus driven by the POMC promoter exhibits impaired whole-body glucose disposal and a defect in glucose sensing in POMC neurons when placed on a high-fat diet (Parton et al., 2007). Thus, the *KCNJ11*polymorphisms could contribute to loss of glucose sensing in both the β cell and POMC neurons, leading to impairment in insulin action, as well as insulin secretion.

The identified polymorphism in PPARγ, which appears to modify susceptibility to type 2 diabetes mellitus and obesity, was identified a decade ago and produces a Pro12-to-Ala (P12A) change in the PPARγ2 gene (Deeb et al., 1998; Beamer et al., 1998). This was

initially confirmed in a meta-analysis (Altshuler et al., 2000) and reconfirmed in the GWA studies. Resistance to diabetes is associated with the minor (Ala12) allele and susceptibility with the major allele (Pro12), which has a prevalence of about 85% among nondiabetic individuals and 88% among diabetic subjects. Exactly how this change in amino acid produces this effect still remains unclear. However, this change occurs specifically in the PPARγ2 isoform of the gene, which is the form specifically expressed in adipose tissue and which is the target of the insulin sensitizing thiazolidinediones (TZDs). Mutations in other functional regions of this gene have also been found in individuals with severe insulin resistance due to familial partial lipodystrophy type 3 (Barroso et al., 1999).

JAZF1, CDC123-CAMK1D, TSPAN8-LGR5, THADA, ADAMTS9, and NOTCH2

Genomic loci near these six genes did not reach significance in the original GWA screens, but their association with type 2 diabetes was confirmed in a large replication study including more than 50,000 individuals, with OR ranging from 1.09 to 1.15 (Zeggini et al., 2008). *JAZF1*, *CDC123/CAMK1D*, and *TSPAN8-LGR5* are associated with small alterations in insulin secretion, whereas the mechanisms linking the other three loci to type 2 diabetes remain uncertain (Grarup et al., 2008).

Additional Loci Associated with Quantitative Metabolic Traits

Mutations in the melanocortin-4 receptor (MC4R) have previously been shown to account for up to 5% of childhood-onset severe obesity (O'Rahilly, 2007), and analysis of the GWAS data has shown a modest, but consistent, association of fat mass and waist circumference with a locus immediately downstream of this gene (Loos et al., 2008; Chambers et al., 2008). Analysis of quantitative traits among the nondiabetic controls of type 2 diabetes GWA studies has also identified variants in the region of the glucose-6-phosphatase catalytic subunit 2 (G6PC2) that function as modulators of fasting glucose, although this effect does not appear to translate into an increased risk of type 2 diabetes (Chen et al., 2008). No consistent associations have been thus far reported with measures of insulin secretion and insulin sensitivity, but further insights are expected from the meta-analyses of the available GWA data.

The Emerging Genetic Architecture of Type 2 Diabetes

Taken together, what do these GWA association studies tell us about the genetics of type 2 diabetes? First, assuming our basic model is correct, these studies suggest that type 2 diabetes may be more heterogeneous and more polygenic than previously believed. While previous reviews had suggested there may be two or three major genetic forms of type 2 diabetes along with some minor forms, the GWA studies would suggest that from a genetic perspective type 2 diabetes represents a very large number of different disorders. This seems a bit at odds with the common clinical presentation of the disease and raises a question as to how these different genetic forms of type 2 diabetes might differ at a clinical level.

The second finding of these studies is the relatively high frequency of each of the risk variants in the population, ranging from 0.26 for TCF7L2 to 0.85 for PPARγ (Table 3). The high frequency of the risk variants together with the small risk of type 2 diabetes conferred

by each allele translate into a very large number of individuals who carry several of the disease variants but do not develop type 2 diabetes. Indeed, one can estimate from the individual allele frequencies that 99% of the population carries nine or more risk alleles, whereas only 8%–10% of the population develops type 2 diabetes. Such low penetrance is consistent with the mild effect of the risk variants, requiring the presence of other factors, presumably environmental, for the development of hyperglycemia. The mild effect may also be explained by the fact that most of these variants are in noncoding regions of the gene, where they may produce only subtle differences in regulation of expression. This scenario contrasts sharply with that of Mendelian forms of diabetes, such as MODY, which are caused by rare mutations in the coding sequence resulting in significant amino acid substitutions or truncated proteins, leading to hyperglycemia even in the absence of other diabetogenic exposures.

The third finding is that the loci identified to date appear to explain only a small proportion of the familial clustering of type 2 diabetes. Indeed, in the WTCCC study, the nine strongest loci together account for only 7% of the 30%–60% increase in the risk of type 2 diabetes typically observed in siblings of type 2 diabetes probands as compared to the general population (Zeggini et al., 2007). If our current genetic models are correct (and this remains an important question), this would suggest that the loci identified to date are just the tip of the iceberg. In each GWA scan, other loci showed significant associations with type 2 diabetes but were not pursued because they were not replicated across multiple studies. While some of these are certainly false positives, some of these are likely genuine effects that need to be explored further.

At least four other hypotheses also need to be considered in interpreting these studies. First, it is possible that our previous estimates of the contribution of genetics to development of type 2 diabetes may be exaggerated by our inability to assess other factors in family and population studies, such as shared environment. Indeed, there are environmental risk factors that may not have been previously appreciated, and compared to our robust approaches to genetic analysis, our techniques for identifying environmental risk factors are still very primitive. Furthermore, critical environmental exposures (e.g., maternal obesity, intrauterine environment, nutritional composition, or differences in intestinal flora) may be subtle and begin as early as intrauterine life, thus altering patterns of development and programming metabolic responsiveness to environmental stimuli during later life. Such concepts are supported by studies of monozygotic twins, in which primary DNA sequence is identical, yet diabetes risk is discordant and linked to birth weight (Poulsen et al., 1999) and by the findings that low birth weight confers increased risk for diabetes equal in magnitude to the effect of the TCF7L2 polymorphism (Cauchi et al., 2006).

Second, our concepts about how genes interact with each other and with the environment may be too simplistic. For example, in a polygenic rodent model of type 2 diabetes created by heterozygous inactivation of both the insulin receptor and IRS-1, there is evidence of a very marked epistasis, such that neither gene defect alone can produce diabetes in more than 10% of mice, but when they occur together, more than 50% of animals develop diabetes at young age (Figure 3A) (Bruning et al., 1997). Furthermore, appearance of “clinical” diabetes in this and other rodent models can be markedly different depending on the genetic

background of the mouse, demonstrating other important gene-gene interactions (Figure 3B) (Almind et al., 2003).

Third, it is possible that the current models of genetics are clouded by our underestimate of the role of epigenetics in disease. In rodent models that mimic low birth weight in humans by food restriction or restriction of placental flow of pregnant dams, it has now been clearly demonstrated that not only do the low birth weight offspring have an increased risk of diabetes, but this risk is passed on to the second generation, probably through effects on intrauterine and early postnatal nutritional effects on genetic imprinting and/or epigenetic regulation of gene expression or development (Sharif et al., 2007; Ozanne and Constancia, 2007; Jimenez-Chillaron et al., 2006). Moreover, these epigenetic marks, while resulting from early life exposures, can actually progress during postnatal life and thus contribute to age-dependent transcriptional repression of key metabolic genes, as has recently been demonstrated for the β cell transcription factor PDX1 (Park et al., 2008) and the insulin-sensitive glucose transporter GLUT4 (Raychaudhuri et al., 2008, Woo and Patti, 2008).

Finally, we need to consider the possibility that our model of the genetics of type 2 diabetes with a moderate number of relatively common polymorphisms causing disease, is wrong. If the genetic component of type 2 diabetes is represented by uncommon (<5% of the population), but highly penetrant, disease alleles, the GWA studies conducted to date would have been limited in their ability to find the disease genes since the current SNP arrays capture only a small fraction of all the rare variants that are estimated to exist in the human genome.

Insights into Pathogenesis from GWA Studies

The GWA association studies continue to open our eyes to the broad nature of molecules that might contribute to the pathogenesis of type 2 diabetes. Clearly many of the genes identified in both GWA and positional cloning studies would not be considered typical “candidate” genes. However, we do need to be cautious about interpreting what these studies tell us about the genes and tissues involved in the pathogenesis of type 2 diabetes. It is especially important to keep in mind that most of the observed associations are in large domains of strong linkage disequilibrium in noncoding regions of the genome. These association signals are usually named as if there are defects in the closest specific gene, but many of these domains contain multiple genes, and thus the “designated” type 2 diabetes gene may or may not be the gene whose expression or function is altered by the polymorphism. Also, in silico analyses predict that up to 50% of conserved *cis*-acting elements in the human genome are up to 1 Mb from target genes, sometimes in the introns of neighboring genes (Vavouri et al., 2006). These predictions have been confirmed by chIP-on-chIP experiments (Carroll et al., 2005) and RACE data from the Encode project (Birney et al., 2007). Thus, the true type 2 diabetes genes may be placed at some distance from the association signals.

With these caveats in mind, it is interesting to note that several of the genes placed in the proximity of GWA signals are expressed in β cells. This, together with the findings of association with glucose-stimulated insulin secretion (Steinthorsdottir et al., 2007; Florez et

al., 2006a; Sladek et al., 2007), has led some to conclude that β cell defects have a more primal role in the etiology of type 2 diabetes than insulin resistance or that changes in muscle oxidative metabolic phenotypes are not genetic in origin. However, this may not be necessarily the case. The focus of the GWA studies on overt type 2 diabetes favored finding genes marking a limitation of β cell function, since ultimately all forms of diabetes could be viewed as having relative insulin deficiency. The identification of variants predisposing to diabetes through effects on insulin sensitivity will require other study designs, such as ones based on association between insulin sensitivity and genotype in the prediabetic state, i.e., before the onset of overt hyperglycemia. Another factor clouding the discovery of potential insulin resistance genes in GWA studies may be the very strong environment-gene interactions for insulin resistance with body weight, physical activity, and other factors, as compared to the potentially purer manifestation of genetic control on insulin secretion.

Implications of GWA Results for the Development of New Diagnostics and Therapeutics for Type 2 Diabetes

One of the major promises of genetic research has been the hope that this will lead us to new diagnostics and therapeutics for disease. The new GWA findings could represent a significant step in this direction, but it is still early to know. With regard to prediction of disease, most of the single loci identified by GWA mark only a 10%–20% increase in risk of disease, and even the strongest single association, *TCF7L2*, represents only about a doubling of disease risk in its homozygous state. Higher relative risks can be generated by combining multiple markers together. Indeed, about 97% of the population carry between 9 and 20 risk alleles at the 15 type 2 diabetes loci identified thus far (Figure 4A). If we assume that these genetic effects are additive, the ~1.5% of the population who have ≥20 risk alleles have a 6-fold increase in the odds of developing type 2 diabetes as compared to the 1.5% who carry ≤9 risk alleles (Figure 4B). In terms of predictive value, this translates into an increment of about 10 percentage points over the probability of type 2 diabetes before the genetic test (from 7%—the prevalence of type 2 diabetes in the population—to 17%, Figure 4C). However, for more common risk categories such as those defined by carrying 17 or 18 risk alleles, the increment over the prior probability is in the order of only 3–5 percentage points (Figure 4C). The predictive value of multiple positive markers could be higher if some of the 15 type 2 diabetes genes interact with each other as one recent report indicates (Cauchi et al., 2008b). However, other studies have not shown such synergistic effects. Thus, at present, even a panel of multiple genes has uncertain usefulness in genetic prediction, and it remains to be seen how this would compare to traditional clinical markers of prediction, such as presence of obesity, family history, ethnic background, history of low birth weight or gestational diabetes, etc.

With regard to therapeutic implications, these risk alleles do point to a number of previously uninvestigated pathways that might alter β cell function, insulin action, or metabolism. Even for variants that have a small effect on type 2 diabetes risk, it is conceivable that the activity of the cellular pathways in which these are placed can be modulated by drugs to a much larger extent than what is observed as the consequence of natural variation. On the other

hand, some of these pathways, such as the Wnt and cell-cycle pathways, are so central to normal cellular growth and function that finding a selective drug target may be difficult.

Looking Forward

Our knowledge of the genetics of type 2 diabetes has come a long way since the days of a few candidate genes studied by means of one or two haphazardly chosen restriction fragment length polymorphisms. Yet, these new findings should be considered as a starting point rather than the arrival. There is little doubt that additional type 2 diabetes loci and genes will be identified through follow-up of “hot spots” in the existing scans (Zeggini et al., 2008) and GWA scans focused on certain ethnic groups and specific clinical or pathophysiological phenotypes of type 2 diabetes.

Also, the current analyses have only considered the effects of individual SNPs in isolation from the effect of other genes or environmental factors. As the effect of these variants becomes increasingly established, attention needs to be focused on genegene and gene-environment interactions. Prospective cohorts for which data are available on dietary exposures, physical activity, and other potential environmental modifiers will be needed to accomplish this task.

Finally, it should be emphasized again that the current GWA studies are based on the “common-disease/common-variant hypothesis” holding that genetic predisposition to common disorders is determined by common genetic variants with small or modest effects (Reich and Lander, 2001). As discussed above, the available genotyping arrays are not designed to investigate the alternative “heterogeneity hypothesis” maintaining that susceptibility to common disorders results from a large number of rare variants, each having a relatively large effect (Pritchard and Cox, 2002). Identification of such rare variants, if they exist, will require resequencing of the entire genome of type 2 diabetes cases and controls. Fortunately, this previously insurmountable task is becoming increasingly realistic with the ongoing development of new, powerful sequencing methods. Likewise, the contribution of structural variants, such as copy-number variants, insertions, deletions, and duplications, could also contribute to genetic susceptibility not explained by single nucleotide substitutions (Feuk et al., 2006). With these additional pieces in hand, we would have a complete view of the genetic architecture of type 2 diabetes. We do not know how the final picture will look, but these initial findings suggest that it will be different from anything we imagined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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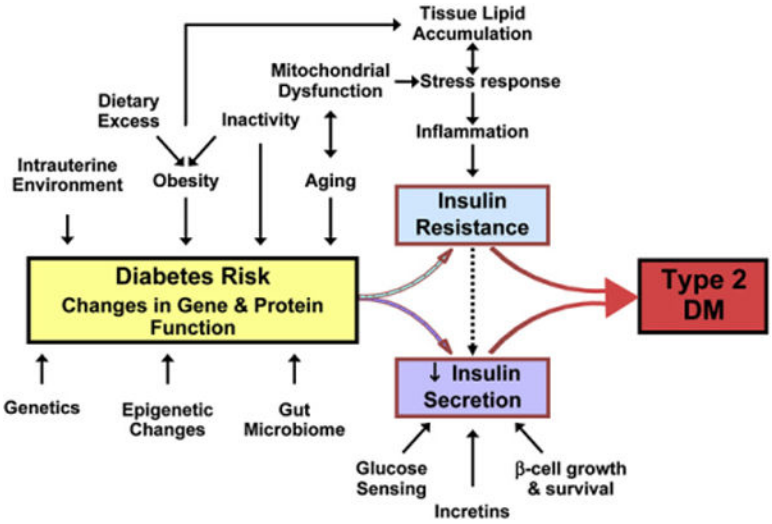

Figure 1. Complex Pathogenesis of Type 2 Diabetes

Genetic and environemntal factors may influence the risk of diabetes through the pathways ilustrated in the figure or through as-yet-unidentifed mechanisms affecting insulin sensitivity and/or insulin secretion.

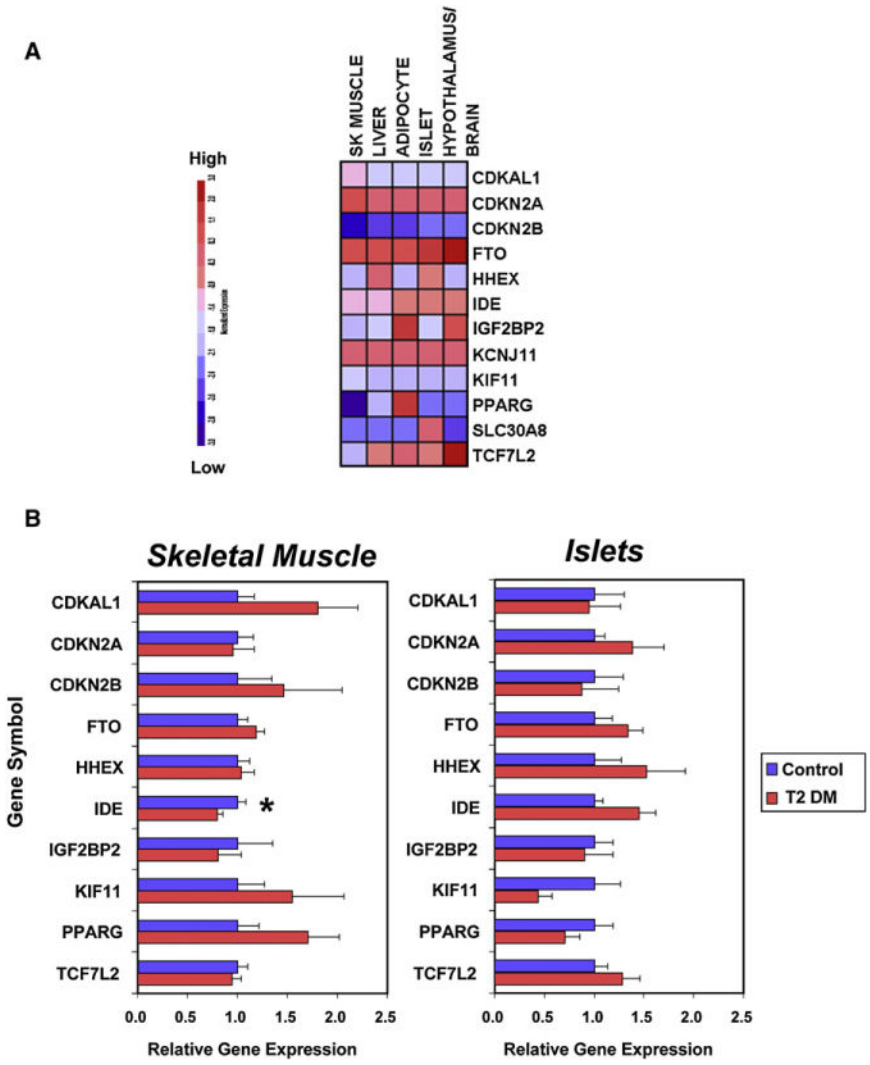

Figure 2. Expression Profiles of Genes Placed at the Type 2 Diabetes Loci Identified to Date

(A) Expression levels across different tissues.

(B) Relative expression levels in skeletal muscle and pancreatic islets from diabetic and nondiabetic subjects. Skeletal muscle expression data were derived from a cohort of metabolically characterized Mexican-American subjects with established DM2, treated with sulfonylureas or lifestyle only (n = 5), and compared with control individuals with normal glucose tolerance (n = 6) (Patti et al., 2003). The data on pancreatic islets were derived from isolated islets purified from five type 2 diabetic subjects and seven normoglycemic controls (Gunton et al., 2005). The mean duration of type 2 diabetes was 5.8 ± 2.1 years, and no subjects were insulin requiring. Mean HbA1c was 7.5 ± 0.5% in the diabetic subjects. RNA was extracted from at least 1000 islet equivalents per subject. RNA was prepared separately for each subject and hybridized to Affymetrix U133A and B microarrays. For each study, cRNA was prepared separately for each subject and hybridized to Affymetrix HuGene FL (muscle) and U133A and B (islet) microarrays. Complete microarray data sets are available on the Diabetes Genome Anatomy Project (DGAP) website (http://www.diabetesgenome.org).

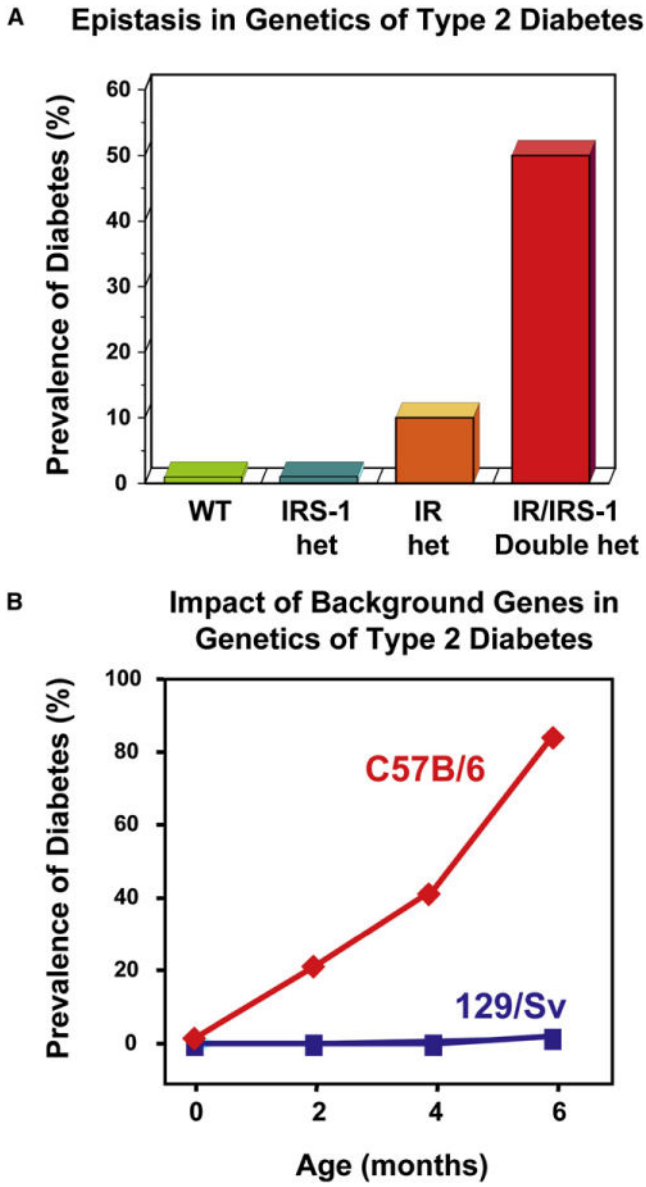

Figure 3. Gene-Gene Interaction in the Etiology of Type 2 Diabetes as Exemplified by Animal Models

(A) Epistasis between insulin receptor (IR) and insulin receptor substrate 1 (IRS1) gene targeting in the development of type 2 diabetes.

(B) Impact of genetic background on the development of type 2 diabetes in mice with genetic insulin resistance.

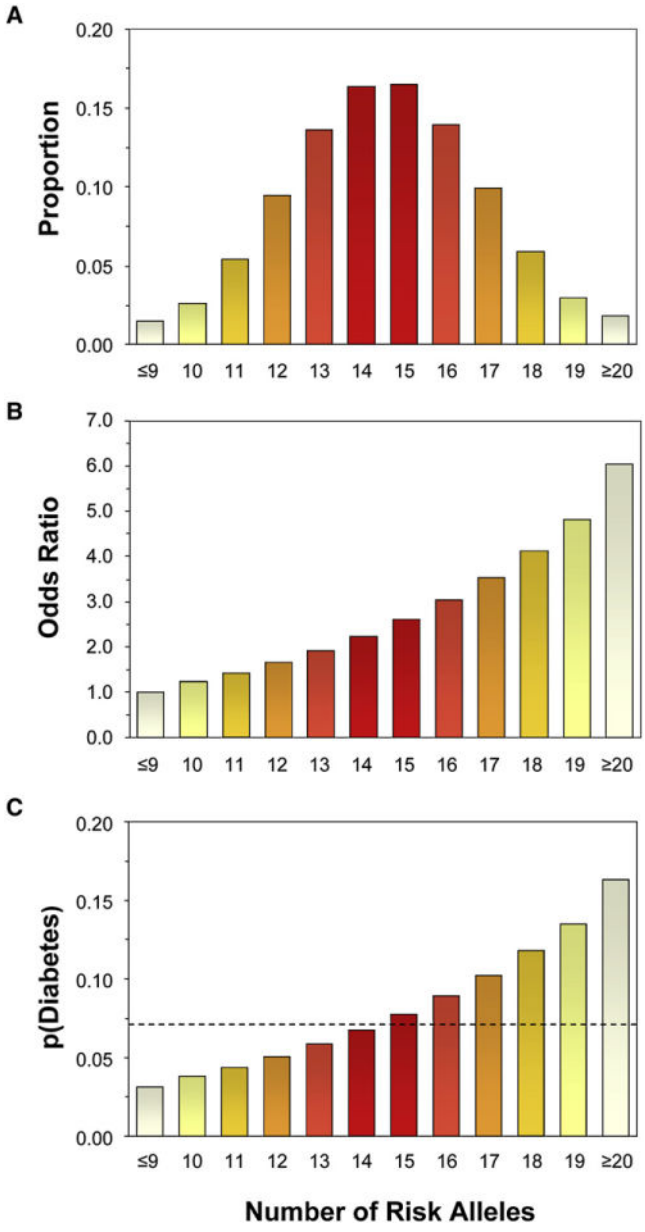

Figure 4. Predictive Value of Multiple Genetic Markers for Type 2 Diabetes

(A) Number of risk alleles carried by individuals from the general population at the 15 type 2 diabetes loci identified to date. Estimates are based on the risk allele frequencies reported in Table 3 and assume independent segregation of the 15 loci.

(B) Odds ratios of type 2 diabetes as a function of the number of risk alleles. The average OR associated with each number of allele was estimated under the assumption of a multiplicative (log-additive) model on the basis of the individual ORs listed in Table 3 and the relative frequencies of the risk alleles in each class.

(C) Probability of type 2 diabetes as a function of the number of risk alleles. Estimates assume an average (pretest) probability of type 2 diabetes of 0.07 (indicated by the dashed line).

Table 1

Identifying the Genes for Type 2 Diabetes

Studies of Monogenic Forms of Type 2 Diabetes
Maturity Onset Diabetes of the Young (MODY)
Rare forms of severe insulin resistance
Neonatal diabetes
Mitochondrial syndromes of diabetes
Candidate Gene Approach
Functional
Genes involved in insulin action and insulin secretion
Genes associated with diseases associated with diabetes (obesity, genetic syndromes, etc)
Genes identified in animal models of diabetes
Positional
Genes in linked intervals identified through family studies
Useful for monogenic forms of diabetes (e.g., MODY)
Challenging for common, multifactorial Type 2 diabetes
Finding Genes with Altered Levels of Expression
Subtraction cloning and differential display
Microarray analysis (gene expression arrays)
Genome-wide Association Studies
Microarray-based typing of ≥ 100K SNPs spanning the entire genome
Large populations of diabetic cases and non-diabetic controls
Populations with intermediate phenotypes – obesity, insulin resistance, polycystic ovarian disease

Table 2

Monogenic Causes of Type 2 Diabetes

Gene Name	Common/Other Name	Cellular Function	Chromosome Location	OMIM Number	Diabetes Phenotype
Monogenic Causes of β Cell Dysfunction					
MODY Diabetes					
HNF4A	HNF4alpha	Transcription factor	20q12	600281	MODY1; β-cell dysfunction
GCK	Glucokinase	Glucose phosphorylation	7p15	138079	MODY2; mild life-long fasting hyperglycemia
TCF1	HNF1alpha	Transcription factor	12q24	142410	MODY3; progressive β-cell dysfunction
PDX1	Insulin promoter factor 1 (IPF1)	Homeodomain transcription factor	13q12	600733	MODY4: Heterozygote: similar to HNF1A (rare); homozygote: pancreatic agenesis and neonatal diabetes
TCF2	HNF1beta	Transcription factor	17q21	189907	MODY5; Renal cysts and diabetes, pancreatic atrophy, neonatal diabetes
NEUROD1	Beta2	bHLH Transcription factor	2q32	601724	MODY6; Similar to HNF1A (rare)
KLF11	Kruppel-like factor 11	TGF-beta inducible Transcription Factor	2p25	610508	MODY7; impairs activation of insulin promoter
CEL	Carboxyl-ester lipase	Lipid metabolism	9q34.3	114840	MODY8; Exocrine and β-cell dysfunction (rare)
Neonatal Diabetes					
KCNJ11	Kir6.2	Potassium channel	11p15.1	600937	Permanent and transient neonatal diabetes
ABCC8	Sur1	Sulfonylurea receptor	11p15.1	600509	Permanent and transient neonatal diabetes
EIF2AK3	PERK	Pancreatic eIF2-alpha kinase	2p12	604032	Wolcott-Rallison Syndrome
PLAGL1	Pleomorhpic adenoma	Plagl1 – Nuclear zinc finger	6p24	606546	Imprinted region, exact gene
HYMA1	gene 1; hydatidiform mole transcript	protein		603044	unclear; transient neonatal diabetes type 1
PTF1A	Pancreas transcription factor 1	Alpha subunit of PTF1	10p12	607194	Permanent neonatal diabetes with cerebellar agenesis
INS	Insulin	Hormone	11p15.5	176730	Mutation in insulin, proinsulin, and proinsulin processing
Mitochondrial Diabetes					

Cell Metab. Author manuscript; available in PMC 2014 December 16.

Gene Name	Common/Other Name	Cellular Function	Chromosome Location	OMIM Number	Diabetes Phenotype
Mitochondrial genome	MIDD	tRNA for leucine	Mutation at 3243 mtDNA	590050	Maternally inherited diabetes and deafness; other mitochondrial mutation also observed
Mitochondrial genome	Mitochondrial myopathy, lipid type	tRNA for glutamic acid	Mutation at 14709 mtDNA	500002	Mitochondrial myopathy with diabetes
Other					
WFS1	Wolframin	10 transmembrane domain protein, function unknown	4p16.1	2223000	Diabetes insipidus and mellitus with optic atrophy and deafness; DIDMOAD; Wolfram Syndrome
ZCD2	ERIS	Zinc finger protein ZCD2	4q22–q24	604928	Wolfram Syndrome 2
Monogenic Causes of Insulin Resistance					
Severe Insulin Resistance					
INSR	Insulin receptor	Receptor tyrosine kinase	19p13	147670	Insulin-resistant diabetes with various phenotypes: leprechaunism, Rabson-Mendenhall or type A syndrome
AKT2	PKB-beta	Serine-threonine kinase	19q1	164731	Severe insulin resistance
Lipoatrophic Forms of Diabetes					
LMNA	Lamin A/C	Inner nuclear membrane protein	1q21	150330	Face-sparing partial lipodystrophy with peripheral fat loss; mutations also associated with cardiomyopathy; muscular dystrophy; and Hutchinson-Gilford Progeria
LMNB2	Lamin B2	Inner nuclear membrane protein	19p13	150341	Partial lipodystrophy sparing legs (Barraquer-Simon Syndrome)
AGPAT2	1-acylglycerol-3-phosphophate O-acyltransferase 2	Enzyme of phospholipid metabolism	9q34	603100	Congenital generalized lipodystrophy with skeletal lytic lesions (Bernardinelli-Seip Syndrome)
BSCL2	Seipin	398 amino acid protein of unknown function	11q13	606158	Congenital generalized lipodystrophy, learning disabilities
PPARG	Peroxisome proliferator activated receptor γ	Nuclear receptor for prostaglands and thiazolidine-diones	3p25	601487	Rare variants in ligand binding domain associated with insulin resistance, hypertension, buttock lipodystrophy

Table 3

Genetic Loci Implicated in "Common Variety" Type 2 Diabetes

Chromosome Location	Gene Symbol	Common/Other name	Cellular Function	OMIM Number	OR	Frequency of Risk Allele
1p12	**NOTCH2**	Notch 2 preproprotein	Regulator of cell differentiation	600275	1.13	*0.11*
2p21	**THADA**	Thyroid adenoma-associated gene	Unknown	611800	1.15	*0.90*
3p14	**ADAMTS9**	Disintegrin-like and metalloproteinase with thrombospondin type 1 motif	Proteolytic enzyme regulating extracellular matrix	605421	1.09	*0.76*
3p25	**PPARG**	Peroxisome proliferator activating receptor gamma (PPARγ)	Transcription factor receptor for TZDs and prostaglandins	601487	1.17	*0.85*
3q28	**IGF2BP2**	IMP2	IGF2 mRNA-binding protein 2	608289	1.14	0.29
6p22.3	**CDKAL1**	CDK5 regulatory subunit associated protein 1-like 1	Presumed regulator of cyclin kinase	611259	1.0–1.20	0.31
7p15	**JAZF1**	Juxtaposed with another zinc finger gene 1	Zinc-finger protein of unknown function	606246	1.10	0.50
8q24.11	**SLC30A8**	ZNT8	Zinc transporter 8	611145	1.18	0.65
9p21	**CDKN2A CDKN2B**	p16 (INK4a) p14(ARF)p15 (INK4b)	Cyclin-dependent kinase inhibitor 2A and 2B	600431	1.20	0.83
10p13-p14	**CDC123**	Cell division cycle protein 123 homolog	Required for S phase entry of the cell cycle	–	1.11	0.18
	CAMK1D	Calcium/calmodulin-dependent protein kinase i-delta	Mediator of chemokine signal transduction in granulocytes	607957		
10q23-q25	**IDE**	Insulin degrading enzyme	Neutral metallopeptidase that can degrade many peptides	146680	1.13	0.53
	HHEX	Hematopoietically expressed homeobox; PRHX	Homeobox transcription factor	604420		
	KIF11	Kinesin family member 11; Homologue of Xenopus EG-5	Kinesin related motor in microtubule & spindle function	148760		
10q25.3	**TCF7L2**	TCF4	High mobility group transcription factor	602228	1.31–1.71	0.26
11p15.1	**KCNJ11**	Kir6.2	Inwardly rectifying potassium channel	600937	1.14	0.47
12q21	**TSPAN8**	Tetraspanin 8	Cell surface glycoprotein	600769	1.09	0.27
	LGR5	Leucine-rich repeat-containing G proteincoupled	Orphan G protein-receptor	606667		
16q12.2	**FTO**	Fat Mass- and Obesity-Associated Gene	58kD protein with nuclear localization signal	610966	1.27	0.38

OR = Odss ratio of type 2 diabetes per risk allele.