REVIEW ARTICLE

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Genomics, Type 2 Diabetes, and Obesity

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Type 2 diabetes, though poorly understood, is known to be a disease characterized by an inadequate beta-cell response to the progressive insulin resistance that typically accompanies advancing age, inactivity, and weight gain.[1] The disease accounts for substantial morbidity and mortality from adverse effects on cardiovascular risk and disease-specific complications such as blindness and renal failure.[2] The increasing global prevalence of type 2 diabetes is tied to rising rates of obesity[2] — in part a consequence of social trends toward higher energy intake and reduced energy expenditure. However, the mechanisms that underlie individual differences in the predisposition to obesity remain obscure.

Failure to understand the pathophysiology of diseases such as type 2 diabetes and obesity frustrates efforts to develop improved therapeutic and preventive strategies. The identification of DNA variants influencing disease predisposition will, it is hoped, deliver clues to the processes involved in disease pathogenesis. This would not only spur translational innovation but also provide opportunities for personalized medicine through stratification according to an individual person's risk and more precise classification of the disease subtype. In this article, I consider the extent to which these objectives have been realized.

Discovery of Susceptibility Genes

For type 2 diabetes and obesity, the discovery of causal genes (Fig. 1 and 2) has followed three main waves. The first wave consisted of family-based linkage analyses (see the Glossary) and focused candidate-gene studies. These proved effective in identifying genes responsible for extreme forms of early-onset disease segregating as single-gene (mendelian) disorders. Genes underlying several distinct, familial forms of nonautoimmune diabetes — including maturity-onset diabetes of the young, mitochondrial diabetes with deafness, and neonatal diabetes — were characterized (see the review by Waterfield and Gloyn[3]). Similar approaches revealed mutations in genes responsible for rare forms of severe childhood obesity, including the genes encoding leptin, the leptin receptor, and proopiomelanocortin (see the review by O'Rahilly[4]). These discoveries have provided insights into processes critical for the maintenance of normal glucose homeostasis and energy balance and clues to the inner workings of the pancreatic beta cell and hypothalamus. For many families, this information has led to improved diagnostic and therapeutic options (described in more detail below).

Attempts to apply similar approaches to families in which either common forms of diabetes or obesity is segregating have proved to be largely unrewarding,[5] and the second wave of discovery involved a switch to tests of association. Although intrinsically more powerful than linkage analysis, association analysis suffers from the disadvantage that the signal can be detected only if one examines

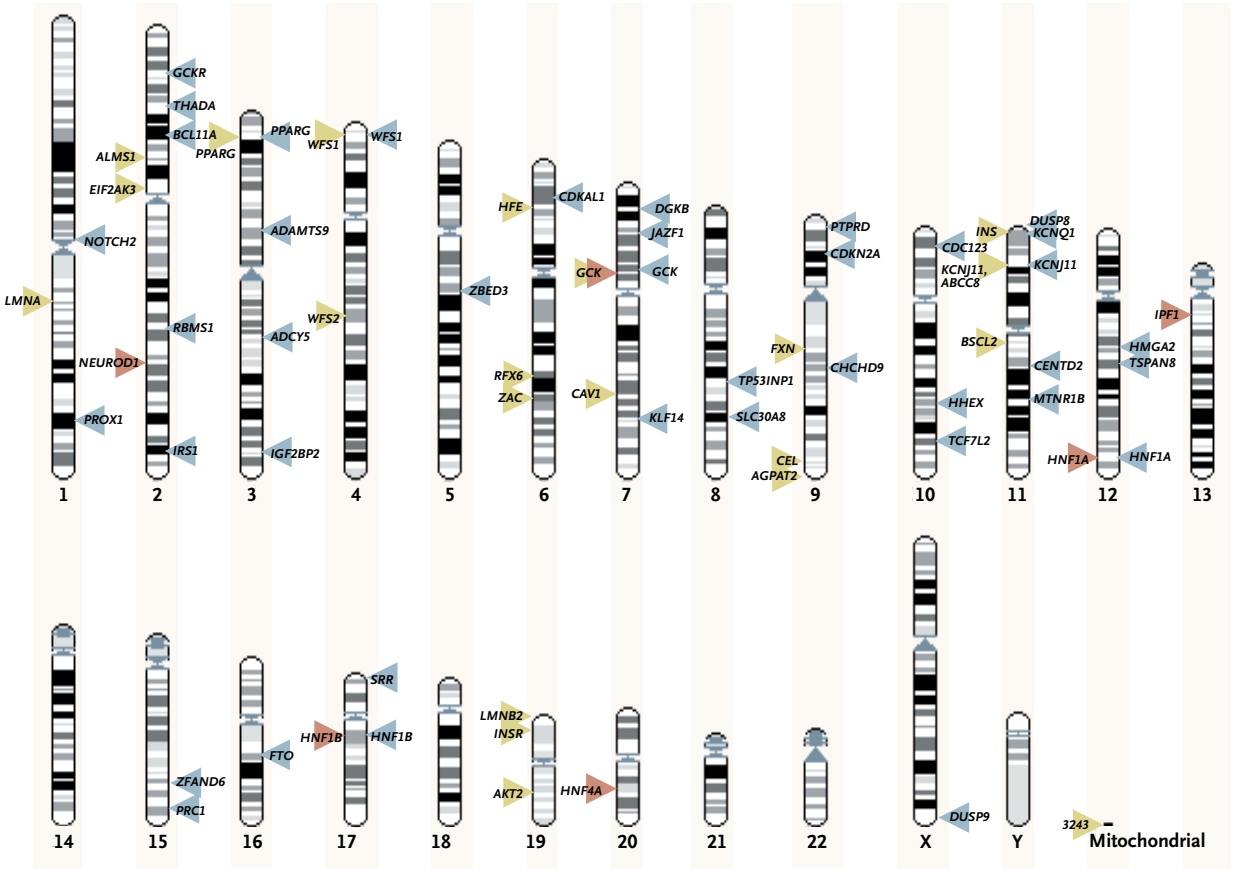

Figure 1. Genomic Locations of Proven Signals of Nonautoimmune Forms of Diabetes.

Signals are shown according to their location on each chromosome. Genes causing monogenic and selected syndromic forms of diabetes are shown to the left: genes implicated in maturity-onset diabetes of the young (red triangles) and those representing loci causal for other monogenic and syndromic forms of diabetes (green triangles). Common variants that have significant genomewide associations with multifactorial forms of diabetes are shown to the right (blue triangles); for these variants, the genes named within the triangles are indicative of signal position, but in most instances, formal proof that these are the specific genes responsible for the association is lacking.

the causal variant itself or a nearby marker with which it is tightly correlated. Until the advent of methods that enabled genomewide surveys of association, researchers were therefore obliged to direct their attention to specific candidate variants or genes of interest.[6] In retrospect, it is obvious that most such studies were seriously underpowered or focused on inappropriate candidates.[6] Nevertheless, by accruing data over the course of multiple studies, some genuine susceptibility variants were identified. Common coding variants in *PPARG* and *KCNJ11* (each of which encodes a protein that acts as a target for classes of therapeutic agents widely used in diabetes management) were shown to have modest effects on the risk of type 2 diabetes.[7,8] Resequencing of the gene encoding the melanocortin-4 receptor (MC4R) resulted in the identification of low-frequency coding variants that explain approximately 2 to 3% of cases of severe obesity.[9]

The third, and most successful, wave of discovery has been driven by systematic, large-scale surveys of association between common DNA sequence variants and disease. The first demonstration that unbiased discovery efforts could reveal new insights into the pathogenesis of type 2 diabetes resulted from identification of the association between type 2 diabetes and variants within *TCF7L2* (encoding transcription factor 7–like 2, a protein not previously identified as a biologic candidate).[10] *TCF7L2* has now been shown to modulate pancreatic islet function.[11]

The number of loci for which there is convincing evidence that they confer susceptibility to type 2 diabetes started to grow in early 2007 with the publication of the first genomewide as-

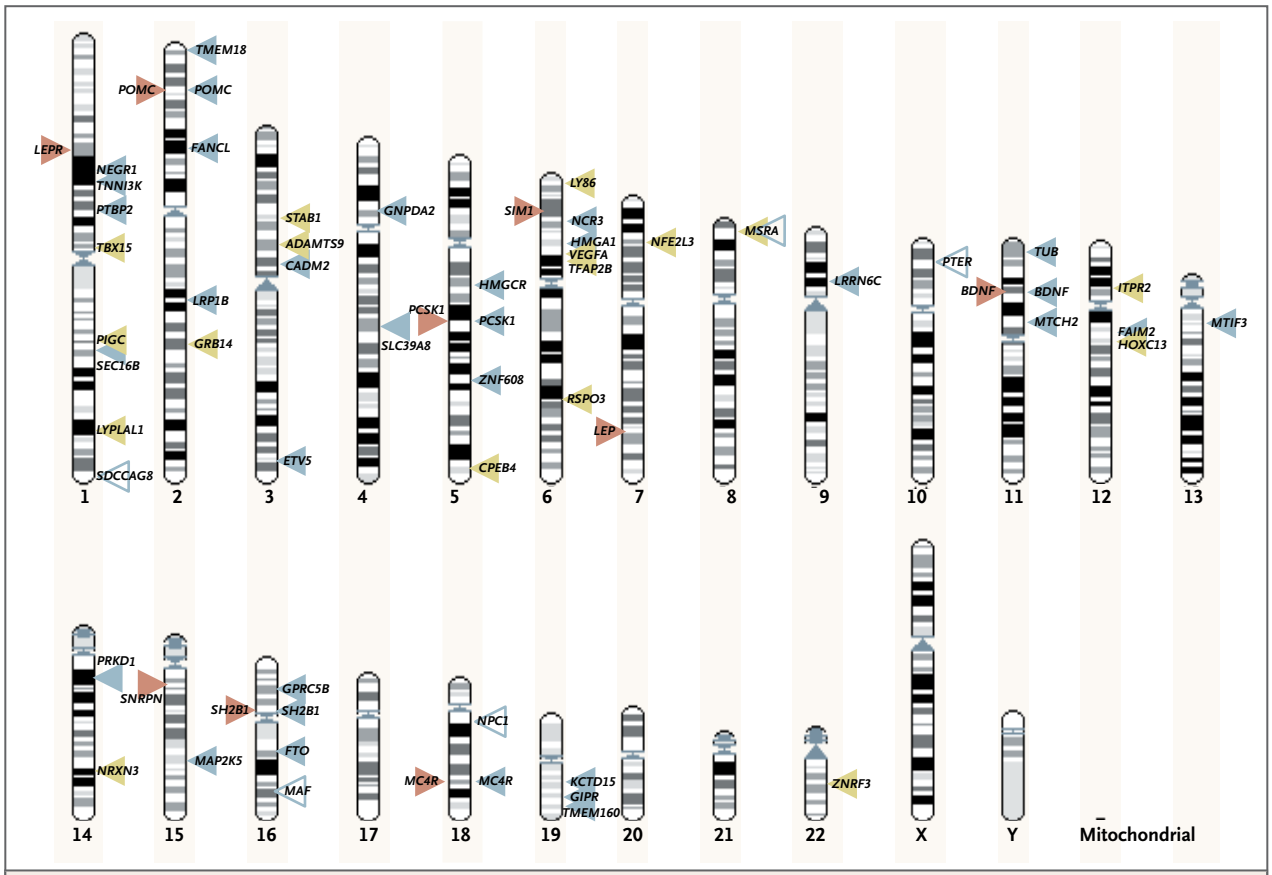

Figure 2. Genomic Locations of Proven Signals of Body-Mass Index (BMI), Obesity, and Related Phenotypes.

Signals are shown according to their location on each chromosome. Genes causing monogenic and selected syndromic forms of obesity (red triangles) are shown to the left. Common variants that have significant genomewide associations with BMI or multifactorial obesity are shown to the right: loci implicated in BMI or weight variation at the population level (solid blue triangles), additional loci identified in case–control analyses of extreme obesity (open blue triangles), and variants identified primarily because of their association with waist circumference or waist-to-hip ratio (solid green triangles). For the variants shown to the right, the genes named within the triangles are indicative of signal position, but in most instances, formal proof that these are the specific genes responsible for the association is lacking.

sociation studies.[12-18] Together, these studies revealed six new associations, including variants near *CDKAL1*, *CDKN2A*, and *CDKN2B* (which encode putative or known regulators of cyclin-dependent kinases) and *HHEX* (which is transcribed into a homeobox protein implicated in beta-cell development). Typically each copy of a susceptibility allele at one of these loci is associated with a 15 to 20% increase in the risk of diabetes. Since then, the dominant approach to discovery has involved ever-larger aggregations of genomewide association data from multiple samples so as to improve the power to identify variants of modest effect: these studies have revealed more than 20 additional confirmed signals of susceptibility to type 2 diabetes[19-22] (Table 1 and Fig. 1). Though early studies were restricted to samples obtained from persons of European descent, genomewide association analyses conducted in other ethnic groups are now emerging.[23,24,29] The current total of approximately 40 confirmed type 2 diabetes loci includes variants in or near *WFS1* (wolframin) and the hepatocyte nuclear factors *HNF1A* and *HNF1B* (genes that also harbor rare mutations responsible for monogenic forms of diabetes)[30-33]; the melatonin-receptor gene *MTNR1B* (which highlights the link between circadian and metabolic regulation)[26-28]; and *IRS1* (encoding insulin-receptor substrate 1), one of a limited number of type 2 diabetes loci with a primary effect on insulin action rather than on secretion.[25]

Genomewide association studies of genetic variants influencing body-mass index (BMI) and

Glossary

Allele: One of two or more versions of a genetic sequence at a particular location in the genome.

Association analysis: An approach to susceptibility-gene discovery that relies on identifying genetic variants whose allele frequencies are robustly correlated with either disease status or the level of a trait of interest.

Candidate-gene study: An approach to susceptibility-variant discovery that focuses on genetic analysis restricted to one or more candidate genes — genes that have typically been selected on the basis of a perceived match between their known or presumed functions and the biologic characteristics of the disease in question.

Coding variant: The part of the genomic DNA sequence that encodes proteins (consisting of approximately 1.5% of the total human genome).

Genomewide association study: An approach used in genetics research to look for associations between many (typically hundreds of thousands) of specific genetic variations (most commonly, single-nucleotide polymorphisms) and particular diseases or traits.

Homozygous: Having the same allele on both chromosomes at a particular location in the genome.

Linkage analysis: An approach to susceptibility-gene discovery that relies on matching family-level patterns of segregation of the disease of interest with genetic markers of known location.

Monogenic disease: Genetic disease attributable to variants with large effects on disease status. Because of the high penetrance of such variants, the disease typically cosegregates in a classic mendelian fashion (e.g., dominant or recessive).

Next-generation sequencing: DNA sequencing that harnesses advances in miniaturization technology to simultaneously sequence multiple areas of the genome rapidly and at low cost.

Noncoding variant: A DNA sequence variant that is located outside the coding sequence; some are likely to be involved in gene regulation.

Syndromic disease: Syndromes are characterized by the concomitant occurrence of several distinct clinical features. In syndromic forms of diabetes such as Wolfram's syndrome, a rare mutation of large effect leads not only to diabetes but also to a diversity of other features including optic atrophy and deafness.

Transcript: An RNA sequence resulting from transcription of a DNA sequence (often a gene).

obesity have been similarly productive, with three main strategies being adopted (Table 2 and Fig. 2). Genomewide association studies of population-based samples to examine the full range of BMI values have identified approximately 30 loci influencing BMI and the risk of obesity. The strongest signal remains the association with variants within *FTO* (the fat-mass and obesity–related gene).[13,34,45] Other signals near *BDNF*, *SH2B1*, and *NEGR1* (all implicated in aspects of neuronal function) reinforce the view of obesity as a disorder of hypothalamic function.[35,37,38,43] A second approach, focusing on case–control analysis of persons selected from the extremes of the BMI distribution, has delivered a complementary, only partly overlapping, set of loci.[39,42,46,47] Finally, genomewide analyses of patterns of fat distribution, prompted by the particularly deleterious health effects of visceral fat accumulation, have characterized approximately 15 loci that are largely distinct from those influencing overall adiposity[36,40,41,44]: many of the 15 display markedly stronger associations in women than in men.

FROM GENES TO CLINICAL PRACTICE

Despite the growing number of loci discovered, the contribution of genetic discoveries to the clinical management of diabetes and obesity remains limited to the small proportion of cases with monogenic forms of disease. What, then, are the obstacles impeding the clinical translation of the scores of multifactorial variants now defined?

The first is the modest effect size of the implicated variants. The common variants with the greatest effects on the risk of type 2 diabetes (*TCF7L2* in Europeans, *KCNQ1* in Asians) result in lifetime prevalence rates that are, in persons carrying two copies of the risk allele, roughly double those seen in persons with none.[10,23,24] The association signal at *FTO* accounts for less than 0.5% of the overall variance in BMI, equivalent to a difference of 2 to 3 kg between adults homozygous for the risk allele and those homozygous for the alternative allele.[13] Most other variants associated with type 2 diabetes and BMI have effects considerably smaller than these. More detailed analysis of the associated regions may reveal that some of these associations are driven by causal variants with larger effects, although empirical evidence supporting this assertion is limited.[22] In contrast, the mutations underlying monogenic forms of diabetes and obesity have far more dramatic clinical consequences: in pedigrees segregating these conditions, knowing whether a family member has inherited a given causal allele generally allows for the confident prediction of disease status.

A second obstacle to the translation of variants implicated in multifactorial forms of diabetes and obesity relates to the speed with which risk-allele discovery has led to an improved understanding of the biologic basis of disease. Most alleles implicated in monogenic and syndromic forms of diabetes and obesity alter the coding sequence and therefore have dramatic

Table 1. Major Genomewide Association (GWA) Studies of Type 2 Diabetes.*

Reference	Sample Size		Major Ethnic Groups	Study Type	Main Findings
	GWA	Replication			
Sladek et al., 2007[12]	1,363	5,511	French	Single GWA study	*HHEX* and *SLC30A8* associations with type 2 diabetes
Scott et al., 2007[14]	2,335	2,473	Finnish	Single GWA study	*CDKAL1*, *CDKN2A*, and *IGF2BP2* associations with type 2 diabetes
Diabetes Genetics Initiative et al., 2007[15]	2,931	10,850	Swedish, Finnish	Single GWA study	*CDKAL1*, *CDKN2A*, and *IGF2BP2* associations with type 2 diabetes
Zeggini et al., 2007[16,18]	4,862	9,103	British	Single GWA study	*CDKAL1*, *CDKN2A*, and *IGF2BP2* associations with type 2 diabetes
Steinthorsdottir et al., 2007[17]	6,674	14,138	Icelandic	Single GWA study	*CDKAL1* association with type 2 diabetes and insulin secretion
Zeggini et al., 2008[19]	10,128	79,792	European	GWA meta-analysis	Six new loci for type 2 diabetes (*NOTCH2*, *JAZF1*, *ADAMTS9*, *TSPAN8*, *THADA*, and *CDC123*)
Yasuda et al., 2008[23]	1,691	18,239	Japanese, Korean, Chinese	Single GWA study	*KCNQ1* association with type 2 diabetes in East Asians
Unoki et al., 2008[24]	1,752	19,489	Japanese, Singaporean	Single GWA study	*KCNQ1* association with type 2 diabetes in East Asians
Rung et al., 2009[25]	1,376	27,033	French, Danish	Single GWA study	*IRS1* association with type 2 diabetes
Prokopenko et al., 2009[26]	36,610	82,689 For type 2 diabetes	European	Follow-up of signals for type 2 diabetes from GWA scan for fasting glucose	*MTNR1B* association with type 2 diabetes and fasting glucose
Lyssenko et al., 2009[27]	2,931	18,831 For type 2 diabetes	Swedish, Finnish	Follow-up of signals for type 2 diabetes from GWA scan for insulin secretion	*MTNR1B* association with type 2 diabetes and fasting glucose
Bouatia-Naji et al., 2009[28]	2,151	15,464 For type 2 diabetes	French, Danish, Finnish	Follow-up of signals for type 2 diabetes from GWA scan for fasting glucose	*MTNR1B* association with type 2 diabetes and fasting glucose
Dupuis et al., 2010[20]	46,186	127,677 For type 2 diabetes	European	Follow-up of signals for type 2 diabetes from GWA scan for fasting glucose	*ADCY5*, *PROX1*, *GCK*, *GCKR*, and *DGKB* associations with type 2 diabetes and fasting glucose
Tsai et al., 2010[29]	1,889	3,276	Taiwanese	Single GWA study	*SRR* and *PTPRD* associations with type 2 diabetes in Taiwanese
Qi et al., 2010[21]	5,643	84,605	European	GWA meta-analysis	*RBMS1* association with type 2 diabetes
Voight et al., 2010[22]	47,117	94,337	European	GWA meta-analysis	12 New loci for type 2 diabetes including *DUSP9*, *KLF14*, *CENTD2*, *HMGA2*, and *HNF1A*

* Only studies in which there were significant genomewide associations with type 2 diabetes are listed.

Table 2. Major Genomewide Association (GWA) Studies of Body-Mass Index (BMI), Risk of Obesity, and Fat Distribution.*

Reference	Sample Size		Major Ethnic Group	Study Type	Main Findings
	GWA	Replication			
Frayling et al., 2007[13]	4,862	38,759	British	GWA study of type 2 diabetes cohort	*FTO* association with BMI, obesity, and type 2 diabetes
Scuteri et al., 2007[34]	4,741	3,205	Sardinian	GWA study of large population isolate	*FTO* association with BMI
Loos et al., 2008[35]	16,876	75,981	European	GWA meta-analysis	Association of common *MC4R* variants with BMI
Chambers et al., 2008[36]	2,684	11,955	South Asian	GWA study of population sample	*MC4R* association with waist circumference
Willer et al., 2009[37]	32,387	59,082	European	GWA meta-analysis	*TMEM18, KCTD15, GNPDA2, SH2B1, MTCH2,* and *NEGR1* associations with BMI
Thorleifsson et al., 2009[38]	34,416	43,651	Icelandic	GWA study of large population isolate	Nine new associations with BMI (*NEGR1, TMEM18, ETV5, BDNF, FAIM2, KCTD15, SH2B1,* and *SEC16B*) or weight (*NCR3*)
Meyre et al., 2009[39]	2,796	14,186	French	GWA study of morbidly obese adults vs. normal-weight controls	Associations of signals near *NPC1, MAF,* and *PTER* with extreme obesity (from case–control analyses)
Lindgren et al., 2009[40]	38,580	70,639	European	GWA meta-analysis	Associations near *TFAP2B* and *MSRA* with waist circumference and near *LYPLAL1* with waist-to-hip ratio
Heard-Costa et al., 2009[41]	31,373	38,641	European	GWA meta-analysis	Associations of *NRXN3* variants with waist circumference
Scherag et al., 2010[42]	2,258	36,734	European	GWA study of persons with extreme early onset obesity vs. lean controls	*SDCCAG8* and *TNKS–MSRA* associations with childhood obesity
Speliotes et al., 2010[43]	123,865	125,931	European	GWA meta-analysis	18 New loci (including *POMC, GIPR,* and *HMGA1*) influencing BMI
Heid et al., 2010[44]	77,167	113,636	European	GWA meta-analysis	13 New loci (including *VEGFA, TBX15,* and *HOXC13*) influencing waist-to-hip ratio independent of BMI

* Only studies in which there were significant genomewide associations with BMI, waist circumference, waist-to-hip ratio, or obesity are listed.

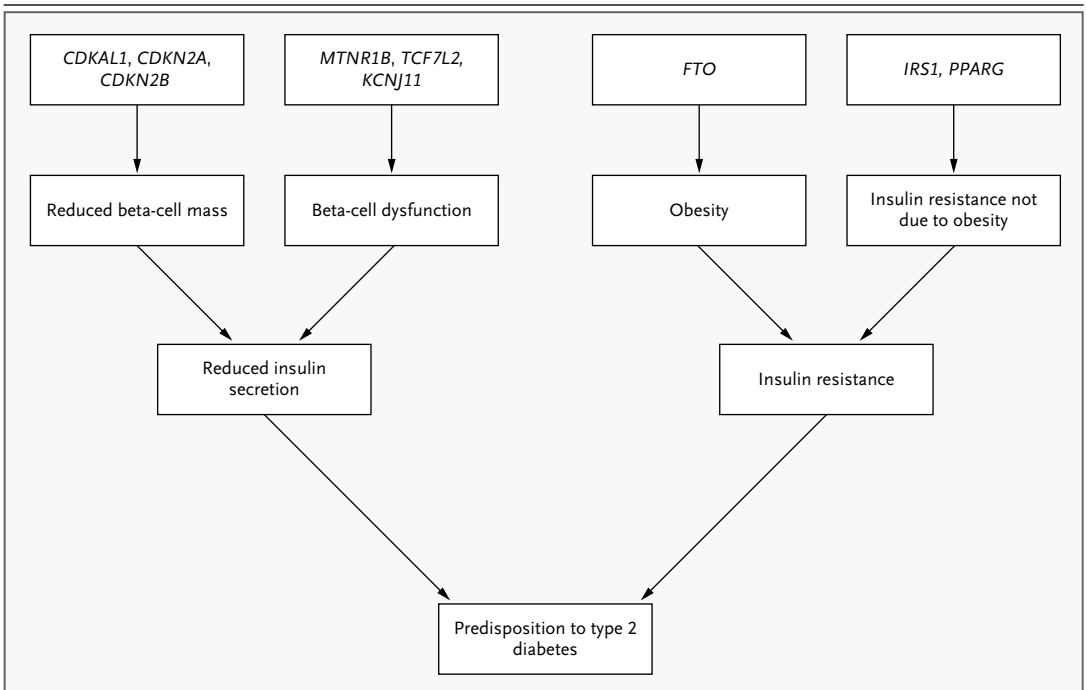

Figure 3. Pathways to Type 2 Diabetes Implicated by Identified Common Variant Associations.

Type 2 diabetes results when pancreatic beta cells are unable to secrete sufficient insulin to maintain normoglycemia, typically in the context of increasing peripheral insulin resistance. The beta-cell abnormalities fundamental to type 2 diabetes are thought to include both reduced beta-cell mass and disruptions of beta-cell function. Insulin resistance can be the consequence of obesity or of obesity-independent abnormalities in the responses of muscle, fat, or liver to insulin. Examples of susceptibility variants that, given current evidence, are likely to influence predisposition to type 2 diabetes by means of each of these mechanisms are shown.

and largely predictable effects on the function of the gene. The use of molecular diagnostics to derive clinically useful prognostic and therapeutic information relies on this relatively straightforward assignment of functional significance. In multifactorial disease, however, most susceptibility variants lie outside the coding regions of genes and are assumed to influence transcript regulation rather than gene function.

Characterization of the downstream consequences of these "noncoding" variants is difficult, given our rudimentary knowledge of the mechanics of gene regulation. Detailed functional studies are required to translate these genomic "signposts" into biologic knowledge that can spur translational development, and there have been relatively few successes.[48] Indeed, at most susceptibility loci, it remains far from clear even which transcripts mediate the susceptibility effects that have been observed.

The time required to achieve clinical translation is often underestimated,[49] and most of the discoveries in multifactorial disease have simply been too recent for their full translational potential to be realized. That potential lies in three main areas: the characterization of disease mechanisms that provide new targets for treatment and prevention, improved risk prediction and differential diagnosis, and personalized treatment and prevention.

FROM GENETICS TO BIOLOGY

An improved understanding of pathophysiology achieved through genetic discovery provides new opportunities for treatment, diagnosis, and monitoring. Studies of risk variants for type 2 diabetes in healthy populations have shown that most variants act through perturbation of insulin secretion rather than insulin action, establishing inherited abnormalities of beta-cell function or mass (or both) as critical components of the progression to type 2 diabetes (Fig. 3).[22,50] (An interactive graphic depicting proposed mechanisms of

An interactive graphic is available at NEJM.org

some susceptibility variants associated with type 2 diabetes is available at NEJM.org.) At loci for which there is evidence of a primary effect driven by abnormalities of insulin action, both obesity-dependent and obesity-independent mechanisms are involved (Fig. 3).[22] As described above, it is not always easy to link association signals to specific transcripts, but some of the genes more confidently assigned to type 2 diabetes susceptibility — *TCF7L2, SLC30A8,* and *CDKN2A* and *CDKN2B* — relate to Wnt signaling, zinc transport, and cell-cycle regulation, respectively, suggesting that these functions have roles in the maintenance of normal islet function.[22,51] Beyond that, efforts to identify key processes in the pathogenesis of type 2 diabetes — for example, by showing that genes encoding members of particular pathways are overrepresented at susceptibility loci — have not been particularly rewarding.[22] Either type 2 diabetes is highly heterogeneous, or those fundamental disease processes are poorly captured by existing biologic knowledge.

Efforts to achieve therapeutic modification of weight have had little success. The identification of new pathways amenable to safe and effective weight manipulation would be a valuable "deliverable" from genetic-discovery efforts. However, the transition from association signal to causal mechanism has not been straightforward, especially when the disease involves tissues as inaccessible to direct study as the human hypothalamus. Consider the example of *FTO*.[13] Although the association signal maps to a clearly defined region of the gene, and the effect is comparatively large, there is still some doubt as to whether *FTO* itself is responsible for the weight phenotype, rather than one of the nearby genes such as *RPGRIP1L* (also expressed in the hypothalamus, with responses to alterations in nutritional and hormonal status similar to those of *FTO*[52]). Studies of mice with disruptions of *Fto* sequence[53,54] are consistent with the hypothesis that *FTO* mediates the BMI effect in humans, whereas studies of human *FTO* mutations have been less clear-cut.[55,56] Notwithstanding these data, the story emerging from the growing number of loci supports the view of overall obesity as a disease of hypothalamic dysregulation.[37,43] In contrast, variation in patterns of fat distribution is associated with variants within genes that influence adipocyte development and function.[40,41,44] How best to use this information to effect early translation into new therapeutic or preventive approaches remains uncertain.

One characteristic of metabolic disease is the cluster of traits referred to as the metabolic syndrome. However, the genetic evidence to date provides limited support for the metabolic syndrome as a defined pathophysiological entity, perhaps indicating that this clustering is driven by environmental factors. Though BMI-associated variants such as *FTO* modulate the risk of type 2 diabetes and hyperlipidemia,[57] and loci altering lipid levels have secondary effects on the risk of coronary artery disease,[58,59] there is little suggestion that the variants implicated in individual components of the metabolic syndrome overlap. At some loci, the patterns of association actually run counter to the broader correlative patterns of the metabolic syndrome. At the glucokinase regulator gene *GCKR,* for example, one common variant allele increases triglyceride levels yet lowers glucose levels.[15,60,61] The complexity of the relations that can exist at the genetic level between closely related phenotypes is further illustrated by the observation that alleles associated with similar degrees of fasting hyperglycemia in healthy populations have highly variable effects on the risk of type 2 diabetes later in life.[20]

PREDICTION AND DIFFERENTIAL DIAGNOSTICS

In cases of monogenic disease, genetic information can provide powerful diagnostic and predictive value for selected patients. Since subtypes of monogenic diabetes and obesity vary in their prognostic implications and therapeutic recommendations, a definitive molecular diagnosis is an important component of clinical management (Table 3).[3,62] To date, the use of molecular diagnostic tools has been limited by the expense of using conventional sequencing technologies to screen known causal genes for mutations that are often specific to a given family. Next-generation sequencing technologies are likely to be transformative in the medium term, though distinguishing pathogenic mutation from incidental variation will remain a challenge. In the meantime, improved biomarkers of diabetes subtypes that enable the more precise targeting of diagnostic resequencing would be valuable. For ex-

Table 3. Initial Treatments for Various Diabetes Subtypes.*

Diabetes Subtype	Causal Genes	Optimal Treatment
Type 1 diabetes	About 40 known (genes in HLA region, *INS*, *PTPN22*, and others)	Lifelong insulin
Type 2 diabetes	About 40 known (*TCF7L2*, *CDKAL1*, and others)	Metformin as primary treatment; also sulfonylureas, glitazones, or insulin
LADA	Genes in HLA region, *INS*, and *PTPN22* (as in type 1 diabetes)	Early recourse to insulin therapy
GCK-MODY	*GCK*	Diet modification
HNF1A MODY	*HNF1A*	Sulfonylureas (low dose)
Mitochondrial diabetes	*MTTL1*	Early recourse to insulin therapy
Lipodystrophies	*LMNA*, *PPARG*, *AGPAT2*, *CAV1*, *BSCL2*, *LMNB2*, and *AKT2*	Uncertain; thiazolidinediones for some subtypes
Neonatal diabetes	*KCNJ11*, *ABCC8*	Sulfonylureas (high dose)
Neonatal diabetes	*INS*	Insulin

* GCK denotes glucokinase, LADA latent autoimmune diabetes in adults, MODY maturity-onset diabetes of the young, and tRNA transfer RNA.

ample, patients with maturity-onset diabetes of the young caused by *HNF1A* mutations have recently been shown to have C-reactive protein (CRP) levels well below those of patients with other subtypes of diabetes, suggesting that CRP could form the basis of a useful diagnostic test.[63] This observation also exemplifies the early translation of genetic discoveries, since it came directly from genomewide association studies showing that CRP levels are influenced by common variants near *HNF1A*.

The effect sizes of the known, common variants influencing the risk of type 2 diabetes and variation in adult BMI are modest, and the proportion of overall predisposition explained is small: approximately 5 to 10% for type 2 diabetes and 1% for BMI.[22,43] As a result, the ability to perform individual-level prediction with respect to these traits is limited. By combining data from multiple loci, one can identify persons who have inherited especially high or low numbers of risk alleles: the risk of type 2 diabetes differs by a factor of approximately 4 between persons in the top 1% and those in the bottom 1% of the "risk-score" distribution.[64-67] However, the risk profiles of many such persons are already discernible on the basis of conventional risk factors (e.g., BMI or family history), and there is limited evidence to suggest that information about genetic predisposition can be used effectively to guide the modification of long-term behavior. The discriminative accuracy of genetic profiling of known type 2 diabetes risk variants (as measured by means of receiver-operating-characteristic curves) is only approximately 60%,[64-67] well below the threshold required for clinical usefulness and the degree of prediction achievable on the basis of nongenetic risk factors.[68] Furthermore, estimates of risk can depend crucially on exactly which variants are included in the risk profile.[69] The key to improved performance will be the identification of risk variants with greater effect sizes than those discovered so far. Since existing genomewide association studies have most likely captured any common variants of large effect, the search is now focused on less-common variants.

A person's risk of type 2 diabetes or obesity reflects the joint effects of genetic predisposition and relevant environmental exposures. Efforts to determine whether these genetic and environmental components of risk interact (in the statistical sense that joint effects cannot be predicted from main effects alone)[70] face challenges associated with measuring relevant exposures (diet and physical activity being notoriously difficult to estimate) and the effect of imprecision on statistical power.[71] Although claims that statistical interactions reflect shared mechanisms (i.e., that the interacting factors act

through the same pathways) are probably overstated, understanding the relative contributions of genetic and environmental components to risk is important. After all, environmental factors can be modified more readily than genetic factors.

Genetic discoveries have provided a molecular basis for the clinically useful classification of monogenic forms of diabetes and obesity.[3,4] Will the same be true for the common forms of these conditions? Probably not: as far as the common variants are concerned, each patient with diabetes or obesity has an individual "barcode" of susceptibility alleles and protective alleles across many loci. It is possible to show that the genetic profiles of lean subjects with type 2 diabetes and obese subjects with type 2 diabetes are not identical, but these differences appear to be inadequate for clinically useful subclassification.[22,72] If efforts to uncover less prevalent, higher-penetrance alleles are successful, more precise classification of disease subtypes may become possible, particularly if genetic data can be integrated with clinical and biochemical information. For example, in persons presenting with diabetes in early adulthood, there are several possible diagnoses: various subtypes of maturity-onset diabetes of the young or mitochondrial diabetes, for example, as well as type 1 or type 2 diabetes. Assigning the correct diagnosis has both prognostic and therapeutic benefits for the patient (Table 3).

TARGETED TREATMENT AND PREVENTION

Recommended therapies for the various subtypes of diabetes differ (Table 3).[3,4,62,73-75] In monogenic forms of diabetes, at least, genetic testing already drives the choice of therapy. For example, in patients who have maturity-onset diabetes of the young due to mutations in the gene encoding glucokinase (GCK), the hyperglycemia is mild and stable, the risk of complications is low, and dietary management is often sufficient. In contrast, in patients who have maturity-onset diabetes of the young due to mutations in *HNF1A*, the disease follows a more aggressive course, with a greater risk of severe complications, but is particularly responsive to the hypoglycemic effects of sulfonylureas.[62,73] Most children with neonatal diabetes have mutations in *KCNJ11* or *ABCC8*, adjacent genes that jointly encode the beta-cell ATP-sensitive potassium channel that mediates glucose-stimulated insulin secretion and is the target of sulfonylureas. In such children, treatment with sulfonylureas has proved more effective and convenient than the lifelong insulin therapy previously considered the default option.[74,75] In children with severe obesity due to profound leptin deficiency, exogenous leptin therapy is lifesaving.[76]

As yet, there are insufficient genetic data to support management decisions for common forms of type 2 diabetes and obesity.[77] Although the *TCF7L2* genotype is associated with variation in the response to sulfonylurea treatment,[78] the effect is too modest to guide the care of individual patients. For the time being, the contribution of genetic information to therapy is most likely to come through the drug-discovery pipeline. Information from genetic studies could be used to identify new targets for pharmaceutical intervention that have validated effects on physiological characteristics, to provide information about new and existing targets (e.g., clues about the long-term safety of pathway intervention),[32] and to characterize high-risk groups to enable more efficient clinical trials of agents designed to reduce the progression of type 2 diabetes or obesity or the risk of complications.

SUMMARY

Given the substantial time it takes to translate basic biomedical discoveries into clinical tools,[49] any current assessment of the clinical value of recent advances in the genetic basis of common diseases is probably an underestimate. An improved understanding of fundamental disease mechanisms is already emerging; this will underpin future therapeutic advances. But the expansion of personalized medicine beyond monogenic forms of disease awaits a more complete description of predisposition. The boundaries of personalized medicine will be much clearer in a few years, after large-scale genomewide resequencing efforts (now under way) provide a systematic, comprehensive description of the relations between genome sequence variation and major clinical phenotypes.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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