Genetic approaches to the molecular understanding of type 2 diabetes

MARK I. MCCARTHY1 AND PHILIPPE FROGUEL2,3
1Imperial College Faculty of Medicine and Medical Research Council Clinical Sciences Centre, Imperial College, London W12 0NN; 2Queen Mary School of Medicine and Dentistry, London EC1M 6BQ, United Kingdom; and 3Centre National de la Recherche Scientifique-8090 Institut de Biology, Institut Pasteur de Lille, 59000 Lille, France

McCarthy, Mark I., and Philippe Froguel. Genetic approaches to the molecular understanding of type 2 diabetes. Am J Physiol Endocrinol Metab 283: E217–E225, 2002; 10.1152/ajpendo.00099.2002.—The appreciation that individual susceptibility to type 2 diabetes (T2D) and related components of the dysmetabolic syndrome has a strong inherited component provides a coherent framework within which to develop a molecular understanding of the pathogenesis of T2D. This review focuses on the main approaches currently adopted by researchers seeking to identify the inherited basis of T2D and the present state of our knowledge. One central theme that emerges is that progress in defining the genetic basis of the common, multifactorial forms of T2D is hindered by etiological heterogeneity: T2D is likely to represent the final common pathway of diverse interacting primary disturbances. Such heterogeneity equally compromises efforts to understand the basis for T2D by use of other approaches, such as cellular biochemistry and classical physiology. Analyses that seek to ally sophisticated physiological characterization with measures of genomic variation are likely to provide powerful tools for redressing the loss of power associated with such heterogeneity.

linkage; linkage disequilibrium; susceptibility genes; positional cloning

AROUND ONE IN TEN people alive today suffers from type 2 diabetes (T2D) or is destined to develop it before he dies (109). T2D and associated components of the dysmetabolic syndrome already represent dominant causes of morbidity and mortality in societies worldwide, yet recent estimates predict a doubling in T2D prevalence by 2025 (109). Large intervention studies and clinical trials, notably the UK Prospective Diabetes Study (98) and the Diabetes Prevention Program (94, 109), have convincingly demonstrated the capacity of preventive and therapeutic strategies to reduce hyperglycemia and indicate that such maneuvers have a positive effect on disease progression and the development of complications. However, the benefits of these interventions seem hard to sustain in the long term (97). New therapeutic and preventive treatments are urgently required, and these are most likely to arise out of rational drug discovery based on a thorough molecular understanding of the fundamental processes determining disease pathogenesis (71).

The recognition that susceptibility to T2D (and related conditions within the dysmetabolic syndrome) has a strong inherited component (41) provides a mechanism for developing such a molecular understanding of the pathogenesis of T2D. Compared with other approaches to the dissection of pathophysiological mechanisms, gene discovery efforts have the merit of establishing chains of causality, since physiological changes result from genomic variation, and never the reverse.

Address for reprint requests and other correspondence: M. McCarthy, IC Genetics and Genomics Research Institute, 2nd Floor, L Block, Imperial College (Hammersmith Campus), Hammersmith Hospital, Du Cane Road, London W12 0NN, UK (E-mail: m.mccarthy@ic.ac.uk).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
FROM GENES TO PHYSIOLOGY

One of the classical routes to the genetic dissection of any inherited trait has been to adopt a positional approach, that is, to attempt to map susceptibility loci purely on the basis of chromosomal location (59). The substrates for such approaches are typically sets of families segregating the trait of interest, and the tools are linkage and linkage disequilibrium (LD) analysis. At the heart of both of these methods is the expectation that genes with similar chromosomal positions will only rarely be separated during meiotic recombination. The analysis of transmission patterns through successive generations (observed in families or inferred in populations) therefore allows researchers to localize susceptibility variants by detecting chromosomal markers that show significant cosegregation with disease (68). When successful, such “reverse genetics” approaches allow susceptibility genes to be identified in the absence of prior assumptions about their biological function (50). The value of such approaches is obvious when, as with T2D, the principal pathogenic mechanisms are not known.

Positional cloning in maturity onset diabetes of the young. The past decade has seen substantial strides in our understanding of the basis of monogenic [maturity onset diabetes of the young (MODY)] and syndromic [e.g., maternally inherited diabetes with deafness (55), myotonic dystrophy (84)] forms of diabetes, often gained through positional cloning approaches.

MODY is a strongly familial form of non-insulin-dependent diabetes displaying clear autosomal dominant inheritance, which usually develops during childhood, adolescence, or young adulthood. The predominant physiological feature is a defect in insulin secretion (33). Through a combination of positional cloning and candidate gene efforts, six MODY genes (MODY1–6) have been identified. These genes encode the enzyme glucokinase (GCK/MODY2) (34) and the transcription factors, hepatocyte nuclear factor-4α (HNF-4α/MODY1) (107), hepatocyte nuclear factor-1α (HNF-1α/MODY3) (99, 100, 108), insulin promoter factor-1 (IPF-1/MODY4) (88, 89), HNF-1β (HNF-1β/MODY5) (49), and neuroD1/β2 (MODY6) (65). Mutations in GCK and HNF-1α predominate, with other MODY subtypes rare in all populations so far examined. Additional MODY genes (so-called MODY-X) undoubtedly exist, since there remains a minority of families (between 16 and 45%) in which MODY does not cosegregate with markers tightly linked to the known loci (20).

The major value of these successful gene discovery efforts has lain in the impetus they have provided to understanding of β-cell development and function. GCK (MODY2) phosphorylates glucose to glucose 6-phosphate in pancreatic β-cells and hepatocytes and plays a major role in the regulation and integration of glucose metabolism (66). The physiological characteristics of subjects with GCK mutations have clearly confirmed GCK as the β-cell glucose sensor, and >100 GCK mutations have been observed in MODY to date (31, 34). The kinetic properties of recombinant GCK proteins have shown that the relative enzymatic activity of mutant proteins is impaired (40), resulting in decreased glycolytic flux (91). This defect translates in vivo as a glucose-sensing defect leading to an increase in the blood glucose threshold that triggers insulin secretion (101) and a right shift in the dose-response curve of glucose-induced insulin secretion (17).

An insulin-secretory defect in the absence of insulin resistance is also a feature of diabetic and nondiabetic carriers of MODY3 (HNF-1α) mutations (18). Over 120 different mutations have been reported within coding and promoter regions of this gene (99, 100, 108). In contrast, only a few kindred with HNF-4α (MODY1)-associated diabetes have been described (62, 107). HNF-4α is a member of the steroid/thyroid hormone receptor superfamily and acts within the same transcriptional network as HNF-1α. Whereas HNF-4α controls the expression of HNF-1α in embryonic endoderm, liver, and pancreatic cells, the tables are turned in pancreatic and intestinal cells. This cellular specificity is explained by an alternate promoter of HNF-4α (known as P2), the importance of which has been independently proved by human and mouse genetic studies (11, 96). A nucleotide substitution within the IPF-1-binding site of P2, which segregates with diabetes in a large MODY family, has been shown to cause a threefold reduction in transcriptional activity (96).

Reports of mutations in HNF-1β (MODY5) were initially restricted to a few families with early-onset diabetes (49). However, it has recently become clear that nondiabetic cystic renal disease is a feature of most HNF-1β mutations and that many subjects with HNF-1β mutations present through the renal clinic. This has led to the description of the previously unrecognized clinical syndrome of renal cysts and diabetes (RCAD) (10). Three discrete renal histologies have been described: oligomeganephronia, cystic dysplasia, and familial hypoplastic glomerulocystic kidney disease (9). Approximately 50% of HNF-1β subjects will develop nonnephropathic end-stage renal failure before the age of 45.

A deletion in the gene for the homeodomain transcription factor IPF-1 (or IDX-1, STF-1, PDX-1) was found to cosegregate with early-onset diabetes in a large consanguineous kindred (89). The index case, who was homozygous for the mutation, was born with pancreatic agenesis, but heterozygous relatives have MODY (88). IPF-1 is known to be critical for the embryonic development of pancreatic islets as well as for transcriptional regulation of endocrine pancreatic tissue-specific genes in adults, such as the insulin, glucose transporter-2 (GLUT2), and GCK genes in β-cells and the somatostatin gene in δ-cells.

The availability of a genetic definition of MODY subtypes has had profound implications for our understanding of this condition. Previous suspicions about heterogeneity within MODY, which had been apparent on clinical grounds (93), have been confirmed through detailed clinical and physiological investigation (18, 69), and the basis for associated phenotypes (such as the renal disease in HNF-1β) has rapidly appreciated.
There is, as a result, a growing clinical need for precise molecular diagnosis in early-onset diabetes, given the therapeutic and prognostic value that such information may provide. However, with current technology, the locus heterogeneity and the high proportion of “private” mutations make diagnostic screening laborious (12, 69).

There is demonstrable overlap between MODY and multifactorial T2D. The proportion of subjects diagnosed with T2D who actually have MODY may be as high as 2–5%. However, misdiagnosis aside, apart from IPF-1 (43, 63), there is no clear evidence that variation in any MODY gene has a substantial impact on individual susceptibility to multifactorial T2D.

Positional cloning in multifactorial T2D. Efforts to extend such methods to the more common, multifactorial forms of T2D have been one of the dominant models of genetics research into this disease (106), but there have been two principal obstacles. First, the power to detect linkage will generally be considerably lower than in the monogenic setting (81). It is axiomatic of any complex, multifactorial trait, such as T2D, that individual susceptibility will be determined by the concerted action of many different genes interacting both with one another and with environmental determinants of disease risk. The consequence is that the magnitude of the genetic effect attributable to any single locus [as expressed in terms of the locus-specific sibling relative risk (80)] is likely to be modest (at best), and very large sample sizes (many hundreds or thousands of families) will be required for reasonable power of detection. The strong genetic effect in type 1 diabetes (T1D) attributable to variation at the major histocompatibility focus HLA, which was readily detected in fewer than 100 families, is very much the exception as far as complex trait susceptibility loci are concerned (23). The second difficulty is that, for late-onset diseases like T2D, ascertainment of the large, multigenerational pedigrees that form the typical substrate for studies of Mendelian diseases is difficult. Alternative strategies have been developed and applied, mostly focusing on the analysis of small nuclear pedigrees and sibships containing multiple affected siblings (23, 106). At the same time, other groups have sought to preserve the power available in the analysis of large pedigrees by focusing on the segregation not of diabetes itself but of intermediate traits implicated in the development of the dysmetabolic syndrome (such as insulin sensitivity and fat distribution) (24, 57). Both approaches have their merits and should provide complementary views of the genetic architecture of T2D.

The number of genome scans for T2D published is now in double figures (16, 61, 106), and, with a similar number of studies (and/or subanalyses) focusing on quantitative intermediate traits, this is a propitious moment to take stock. The clearest message is that there is no susceptibility locus of overweening effect for T2D (akin to HLA in T1D). In many ways, this comes as no surprise, since the modest sibling relative risk associated with T2D (~3.5 in Europeans) sets an upper bound to the expected effect size of any single contributory locus. The second conclusion is that, with a few exceptions described below, replication of positive findings between genome scans has proven an infrequent event. It is important to appreciate the likely reasons for this. Given the modest effect sizes expected (locus-specific relative risks ~1.3–1.5), even the largest studies are somewhat underpowered and cannot be guaranteed to detect every locus of modest effect that is segregating in the population studied (48). Even a “carbon copy” genome scan performed in a second data set ascertained under the same framework from the same population will not, for stochastic reasons, produce exactly the same pattern of linkage peaks. The prospects for replication are further compromised by the diversity of ethnicities, ascertainment criteria, diagnostic approaches, and statistical methods employed in different scans (70). With all of these factors serving to diminish the prior likelihood of detecting replication, it is clear that obtaining robust confirmation of linkage within a given region provides strong validation that a susceptibility effect has indeed been localized.

Among regions with the strongest claims for replication are chromosomes 12q (27, 61, 64, 85), 20q (13, 39, 54, 110), 1q (29, 46, 88, 103, 106), 8p (16, 29, 106), and 3q (47, 57, 109). All of these regions are currently subject to positional cloning efforts to identify the etiological variants. To give one example, the 1q21–24 region first came to attention through a subanalysis of genome scan data from young-onset Pima Indian families (46). Corroboration followed in Utah Mormon (29) and Amish families (86). In multiplex French pedigrees (103), evidence for linkage to 1q was particularly strong in leaner subjects, and further replication was evident in analysis of >700 pedigrees from the UK Warren 2 genome scan (106). All of these 1q linkage peaks map within 15–20 cM, well within the limits of localization possible in such studies (82).

Linkage alone has limited power to resolve susceptibility gene location, and the regions that emerge from these scans are typically large, on the order of 10–20 Mb. Identifying the etiological variant(s) underlying the linkage signal within such large regions remains a challenging task, but one which, as recent successes have demonstrated (50, 51, 74, 75, 79), is becoming increasingly tractable. Among the developments that have transformed the prospects for such positional cloning efforts include advances in bioinformatics [the availability of draft human sequence (53)], in genetic epidemiology [an improved understanding of patterns of linkage disequilibrium in human populations (76)], in technology [particularly, robust high-throughput tools for single nucleotide polymorphism (SNP) genotyping (58)], and in the sophistication of statistical analysis [notably, improved tools for association mapping (73, 92)].

The principal tool used to refine the location of susceptibility genes within such regions is linkage disequilibrium (LD) analysis, which exploits the cumulative history of recombination within populations to provide much finer localization than is possible through the
analysis of observed recombination events within families alone (59). There is considerable active debate concerning the most effective strategies for LD mapping within large genomic regions (77, 78, 104), the uncertainty largely reflecting current ignorance as to how susceptibility gene variation maps onto background patterns of LD in outbred populations. Most groups seeking to clone such susceptibility regions are pragmatically following a combination of indirect and direct LD mapping approaches. The former strategy involves fishing for LD using a dense “net” of markers, distributed across the region, whereas the latter focuses on variant detection and association analysis within the strongest positional candidates. Both approaches expect to benefit from the development of increasingly dense SNP maps (95), and from plans to derive a “haplotype” map of the human genome (76). There is, in addition, increasing confidence that such resources may, in the future, provide a basis for efforts to map complex trait susceptibility genes through genome-wide linkage disequilibrium analyses (81, 83).

There is no “roadmap” for the identification of complex trait loci; indeed it seems highly improbable that there is a universal strategy that will optimize mapping of all loci for all diseases in all populations. Nonetheless, valuable insights can be gained from gene discovery successes such as the identification of variation within the gene for calpain-10 as the likely basis for the chr-2q T2D susceptibility effect first seen in a genome scan of Mexican-American sibships (44, 50). Although replication of this original linkage in other populations was limited, LD analyses in Mexican-American cohorts (facilitated by the strong background LD arising from recent genetic admixture) were rewarded with identification of a smaller area of 2q (~250 kb) showing marked association with disease (50). Within this interval, the strongest association was with an intronic SNP in the gene encoding calpain-10, a ubiquitously expressed protease with few prior credentials as a T2D candidate. Subsequent analyses have suggested that several variants within the gene combine to influence individual susceptibility to T2D (21, 30, 50). The contribution of this locus to overall T2D susceptibility appears to be significantly less in Europeans than in Mexican-Americans (21, 30).

The calpain-10 story is, of course, far from over. There remains the (diminishing) possibility that variation in the CAPN10 gene is not itself etiological and that the calpain-10 association instead reflects the action of a nearby variant with which it is in LD (2). Extensive analysis of LD on 2q is attempting to address this question (21). The more interesting question relates to the mechanisms whereby differences in the expression and/or function of calpain-10 translate into an increased risk of T2D, and here the focus has moved to detailed studies of the cellular and physiological consequences of perturbing calpain-10 activity in model systems (2).

Positional cloning in animal models. Animal models of T2D have obvious advantages for positional cloning efforts, including the capacity for detailed ex vivo physiological (and histological) analysis of target tissues (90). Even if the loci underlying diabetes in a given rodent model play no significant role in determining human susceptibility, novel pathways of interest may be highlighted. Analyses of many mouse and rat models of diabetes are currently in progress, with large crosses designed to identify chromosomal regions of interest, typically followed by application of congenic methods to narrow the region and move toward identification of the etiological gene. For example, in the Goto-Kakizaki rat, an excellent polygenic model of T2D, several regions influencing diabetes and related intermediate traits have been identified (36, 37) and susceptibility genes provisionally identified (32). These analyses have illustrated the exquisite complexity of the genetic control of metabolic function, with different loci, for example, seen to influence fasting and postprandial glucose levels. This emphasizes once again the importance of maximizing the physiological information obtained from the subjects recruited to human linkage studies.

As the various genomic regions described above yield up their secrets in coming years, the hope is that, as with MODY, it will be possible to reconstruct the pathophysiological architecture of T2D and to develop ways in which this information can be used to deliver improved patient care.

FROM PHYSIOLOGY TO GENES

The second “classic” paradigm for gene identification has been the “candidate gene” approach. Given advances in the range of tools available for genome-wide analysis of the transcriptome, proteome, and metabonome, the number of plausible candidates is large and growing. The strongest candidate genes are likely to be those supported by multiple lines of evidence, including chromosomal localization to regions of linkage defined in family studies. The major obstacle to the interpretation of candidate gene studies in T2D (as in other traits) has been the proliferation of reports from small studies, often with inadequate study designs. These have oftentimes resulted in isolated reports of positive associations that have proved difficult or impossible to replicate. The promulgation of new “industry standards” for association studies in multifactorial disease (3, 19, 22, 26) should help to remedy these methodological shortcomings. The aim should be to generate data that have power both to detect and, more importantly in many ways, given the low prior probability that any chosen candidate will influence disease susceptibility, to exclude association with confidence.

The literature on the myriad of candidate genes so far studied is undoubtedly distorted by reporting bias (56), making a synthesis difficult. However, most in the field would accept that a strong case can be made for a susceptibility role of variants in the genes for the peroxisome proliferator-activated receptor-γ (PPARγ; see Candidate genes from the adipocyte), insulin (see Role of variation in the insulin gene), the sulfonylurea receptor (45) and its genetic and cellular neighbor the
ATP-sensitive K⁺ channel Kir6.2 (42), insulin receptor substrate-1 (1), and IPF-1 (the only example to date of a MODY gene that may also influence typical T2D susceptibility) (43, 63). Promising data are emerging from studies of the adiponectin gene and PGC-1 (see *Candidate genes from the adipocyte*). The data for these and other candidates have been extensively reviewed elsewhere (41); therefore, this review will focus on two areas of current interest.

**Role of variation in the insulin gene.** The insulin gene is the archetypal β-cell candidate, among the first to be studied for a role in T2D, not least because a large polymorphic minisatellite repeat immediately upstream of the gene (the variable number tandem repeat, or VNTR) was readily amenable to typing using the technologies available at the time. The VNTR remains the focus of our interest within this gene even now, some two decades on, as it is clear, largely from studies of T1D, that it is not simply a useful marker polymorphism but also plays a functional role by regulating transcription of the INS gene and its immediate 3′ neighbor, the gene for the insulin-like growth factor, IGF-II (7). In non-African populations, the diversity of VNTR alleles can be summarized as a bimodal system, with ∼70–75% of chromosomes (“class I alleles”) having a few dozen repeats, the remainder a few hundred (“class III alleles”). It is now firmly established that class III alleles are protective in T1D, a phenomenon thought to relate to different levels of thymic expression of insulin, with consequent differential effects on the generation of tolerance (7). There had been the suspicion, based on small case-control studies in the 1980s, that the susceptibility effects in T2D might be reversed, with class III alleles conferring T2D susceptibility (7). This fits well with (limited) transcription data suggesting that the class III VNTR allele is associated with reduced INS expression. Studies in parent-offspring trios ascertained for T2D have confirmed these suspicions but have shown that the class III-dependent T2D-susceptibility effect is restricted to the paternally derived allele (52). Similar parent-of-origin effects have now been reported at this locus in several other T2D-related traits including polycystic ovarian syndrome (8), childhood obesity (60), and early growth (38).

The obvious conclusion is that these parent-of-origin effects are related to the maternal imprinting of this region. In many tissues, expression of IGF-II [and almost certainly of INS, too, at least in early development (72)] is restricted to the paternally derived allele, providing a simple explanation for paternally restricted susceptibility effects. One intriguing corollary is that these data may indicate, because imprinting in this region is most marked in early development, that the T2D susceptibility effect at INS is established very early in life. If so, it raises interesting parallels with the “fetal origins” hypothesis, which attributes observed associations between restricted fetal growth and adult metabolic disturbance to the long-lasting effects of poor fetal nutrition. It may point to a common mechanism whereby genetic and environmental determinants interact to influence diabetes susceptibility through effects during early development. The observation that variation at VNTR influences birth weight (25) lends some succor to this view, although interpretation is complicated by the fact that class III alleles, contrary to expectation, appear to be a feature of large, rather than small, babies (67).

**Candidate genes from the adipocyte.** Adipose tissue was, until recently, considered an organ dedicated exclusively to energy storage. The discovery of leptin has transformed that view and excited interest in the role of adipocyte-secreted signals in the control of energy balance and metabolism. It is now recognized that the adipocyte has a complex endocrine function, modulating metabolism and playing a key role in the genesis of the dysmetabolic syndrome.

Building on these physiological insights, genetic studies have identified several adipose-expressed genes likely to be contributing to individual risk of T2D and related phenotypes. The strongest evidence implicates the gene for PPARγ. Rare variants that severely decrease the transactivation potential have been found to cosegregate with extreme insulin resistance, diabetes, and hypertension in two families with autosomal dominant inheritance (6). Interestingly, given the proposed role for PPARγ in adipogenesis, affected family members had no evidence of lipodystrophy or abnormal fat distribution. In addition, a common amino acid polymorphism (Pro12Ala) in PPARγ has been associated with T2D (3): homozygous carriers of the Pro12 allele are more insulin resistant and have a 1.25-fold increased risk of developing T2D. There is evidence for an interaction between this polymorphism and the response to elevated free fatty acid (FFA) levels (87). These findings have understandably evoked interest in genes known to influence PPARγ function, and a common Gly482Ser polymorphism in the gene for PGC-1, a transcriptional coactivator of a series of nuclear receptors including PPARγ, has been associated with a 1.34-fold relative risk of T2D (28), although there is no indication of interaction with the PPARγ Pro12Ala variant.

Another recent candidate is the APM1 gene, encoding the differentiated adipocyte-secreted protein ACRP30/adiponectin, an adipokine abundantly present in plasma. The purified COOH-terminal domain of adiponectin has been reported to protect mice on a high-fat diet from obesity and to rescue obese or lipodystrophic mouse models from severe insulin resistance by decreasing levels of plasma FFA and enhancing lipid oxidation in muscle (35). Moreover, plasma levels of adiponectin have been shown to be decreased in obese diabetic subjects and to correlate with insulin sensitivity (4), which makes APM1 an attractive candidate gene for fat-induced metabolic syndrome and T2D. APM1 maps to the region of 3q linked to T2D (47, 103) and the dysmetabolic syndrome (57). Initial indications are that variation within APM1 may modulate adiponectin plasma levels and insulin sensitivity and contribute to an increase in the risk for T2D (47), although further work is required. Additional fat-secreted pro-
teins like secretin, interleukin-6, tumor necrosis factor-α, or plasminogen activator inhibitor-1 represent additional attractive candidate genes for insulin resistance associated with obesity.

INTEGRATING PHYSIOLOGY AND GENETICS

It is clear, as reflected in the growth of new terms such as physiological genomics and integrative physiology, that scientific progress in the understanding of multifactorial metabolic conditions such as T2D and obesity increasingly calls for integration of physiological and genetic approaches. Several factors are contributing to the momentum in this direction.

First, it is increasingly evident that latent pathophysiological heterogeneity has a withering effect on the power of both physiological and genetic approaches to the discovery of etiological pathways. Attempts to reduce such heterogeneity through stratification approaches that permit either detailed physiological measurements to be performed on genetically defined subsets (17, 18, 101) or, equally, genetic analyses on physiologically defined strata (64, 103, 106) may enhance capacity to tease out complex genotype-phenotype correlations. Multivariate approaches to genetic analysis designed to allow combined analysis of multiple physiological parameters (5, 14, 24, 57, 90, 105) have similar objectives.

Second, the increasing power and genome-wide reach of transcriptional, proteomic, and metabolomic analyses provide a multidimensional “bridge” from the genomic to the physiological. Researchers now have access to multiple, complementary, intercorrelated descriptions of the cellular and metabolic status of an organism, which are far richer and far more complex than simple, discrete notions of physiological state (such as insulin resistance or diabetes) (102). Integrating the information from such diverse representations is a challenge but holds great promise. For example, such integration may, by relating typically noisy transcriptional data to contemporary or subsequent metabolic and physiological events, allow those transcriptional changes that are consequential (e.g., those that reflect a given sequence variant) to be distinguished from those that are merely stochastic or epiphenomenal.

Finally, much of the work integrating physiological and genomic approaches will, initially at least, be conducted in animal models. The power of such research will inevitably be accelerated by current developments in the provision of improved rodent genomic resources, high-throughput projects to generate new disease models, and more sophisticated phenotyping tools (15).

T2D remains an enigma: a strongly inherited, quintessentially metabolic trait that has yielded its secrets only slowly to genetic researchers and physiologists. There is, however, every prospect, given the range of tools now available to researchers, that recent success in the dissection of monogenic and syndromic forms of diabetes will be followed by improved understanding of the molecular basis of the more common, multifactorial forms of this disease.

REFERENCES


