Progress in defining the molecular basis of type 2 diabetes mellitus through susceptibility-gene identification

Mark I. McCarthy*

Robert Turner Professor of Diabetes, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital Site, Old Road, Headington, Oxford OX3 7LJ and Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK

The rapid increase in the prevalence of type 2 diabetes (T2D) represents a major challenge for health care delivery worldwide. Identification of genes influencing individual susceptibility to disease offers a route to better understanding of the molecular mechanisms underlying pathogenesis, a necessary prerequisite for the rational development of improved preventative and therapeutic methods. The past decade has seen substantial success in identifying genes responsible for monogenic forms of diabetes (notably, maturity-onset diabetes of the young), and, in patients presenting with early-onset diabetes, a precise molecular diagnosis is an increasingly important element of optimal clinical care. Progress in gene identification for more common, multifactorial forms of type 2 diabetes has been slower, but there is now compelling evidence that common variants in the *PPARG*, *KCNJ11* and *CAPN10* genes influence T2D-susceptibility, and positional cloning efforts within replicated regions of linkage promise to deliver additional components of inherited susceptibility. The challenge in the years to come will be to understand how T2D risk is influenced by the interaction of these variants with each other and with pertinent environmental factors encountered during gestation, childhood and adulthood; and to establish how best to apply this understanding to provide individuals with clinically-useful diagnostic, prognostic and therapeutic information.

INTRODUCTION

As least one in 10 people alive today are destined, on current trends, to develop diabetes at some point during their lifetimes. The total number of individuals with diabetes worldwide (most of it type 2 diabetes, T2D) is scheduled to double in a generation, from 150 million in 2000 to 300 million by 2025 (1). Many millions more are exposed to the increased risk of cardiovascular disease that results from lesser degrees of disturbed glucose metabolism (2). Available medical therapies are usually able to ameliorate the condition, but only rarely restore completely normal metabolism, leaving many patients exposed to debilitating and life-threatening complications (3). Furthermore, while lifestyle modification (weight reduction, more exercise) has been shown to forestall, and even prevent, development of diabetes in susceptible individuals (4), such manoeuvres are notoriously difficult to sustain and seem to have done little, to date, to stem the tide of the diabetes 'epidemic'.

Whereas the pathophysiological basis of type 1 diabetes (autoimmune destruction of the pancreatic beta-cells) is established, considerable uncertainty surrounds that of T2D. This is a disease of relative, rather than absolute, insulin deficiency, in which the pancreatic beta-cells become progressively less able to secrete sufficient insulin to maintain normal carbohydrate and lipid homeostasis (5). Typically, there is concomitant insulin resistance (that is, a tendency for tissues such as fat, muscle and liver to show reduced sensitivity to the metabolic effects of circulating insulin), due to and/or exacerbated by the effects of aging, obesity and reduced exercise (6). However, many important pathophysiological questions remain unanswered, such as the nature of the mechanisms that underlie the relationship between obesity and insulin resistance, the balance between primary defects in lipid and carbohydrate metabolism, and the relative impact of intrinsic and extrinsic factors contributing to beta-cell dysfunction (5–7). Consequently, the fundamental molecular events remain shrouded in mystery.

*To whom correspondence should be addressed. Tel: +44 1865857219; Fax: +44 1865857217; Email: mark.mccarthy@drl.ox.ac.uk

The rapid secular trends in T2D prevalence clearly reflect the global transition towards environments permissive for the development of 'diabesity' (1). At the same time, familial aggregation, twin and migration studies, and analyses in admixed populations provide ample evidence that individual susceptibility to this condition also reflects genetic variation (8). This has now been confirmed by linkage studies in human and animal models and, most directly, by increasing success in identifying the specific genes responsible (see below).

In the face of such dynamic secular environment changes, and substantial ethnic differences in genetic susceptibility (1), it is unrealistic to derive a single measure of heritability for this condition. Moreover, genetic and environmental effects are intimately related and interact throughout life. This is well illustrated by the recent focus on the possible role of early (intrauterine) events in the development of T2D. Building on the observation that small babies are at greatest subsequent risk of T2D and other metabolic and cardiovascular conditions, it has been proposed that poor intrauterine nutrition generates long-standing effects on disease risk through metabolic 'programming' (9). There is considerable support for this 'thrifty phenotype' hypothesis from studies in rodent models (10), although direct evidence of relevance to human disease has been harder to obtain (11–13). A complementary explanation for such 'life-course' associations is provided by possible pleiotropic effects of genetic variation (14). For instance, insulin is a major determinant of early growth, and also plays a central role in maintaining glucose homeostasis: thus, genetic variation that compromises the function and/or expression of key components of the insulin secretory (or insulin signalling) pathways could both limit early growth and increase subsequent T2D risk, helping to explain the observed associations (15). There is growing evidence from human studies that this is indeed the case (16–18). In practice, it is probable that fetal genotype, maternal genotype and intrauterine environment all play their part in influencing birth weight and in providing the 'early-origins' component of individual T2D risk.

LESSONS FROM MONOGENIC AND SYNDROMIC FORMS OF DIABETES

The past decade has seen spectacular advances in the identification of genes responsible for monogenic and syndromic forms of diabetes (Table 1). For these conditions, Mendelian segregation and access to large multigenerational families have facilitated classical positional cloning strategies.

Under current schemas for diabetes classification, the term 'type 2 diabetes' specifically excludes subtypes with defined genetic aetiologies (19). However, the close clinical, physiological and genetic overlap between these monogenic and/or syndromic forms of diabetes and more common, multifactorial T2D, indicates that understanding of the former—even though collectively they account for less than 5% of diabetes—is likely to be highly relevant to the latter (20). The most valuable insights have arisen through study of families with maturity-onset diabetes of the young (MODY) (21). It was recognized, three decades ago, that a subset of subjects with early-onset diabetes did not have type 1 diabetes (the subtype of diabetes usually associated with presentation in early life), but instead displayed a clinical course otherwise redolent of type 2 diabetes (or maturity-onset diabetes, as it was then known) (22). Inheritance patterns often suggested dominant Mendelian segregation, although marked clinical differences between families hinted at locus heterogeneity (22). These inferences have been substantiated by the identification, through positional cloning and candidate-gene-based analyses, of six different MODY genes (23–29) (Table 1). Collectively, these account for causation in close to 90% of MODY families (21).

Since the predominant phenotype in MODY is a defect in insulin secretion (one important difference compared to multifactorial T2D is the relative absence of insulin resistance and obesity), it is no surprise that these genes exercise their primary effect on the beta-cell. The *GCK* gene, for example, encodes the enzyme glucokinase, which acts as the beta-cell's glucose sensor (30): haploinsufficiency leads to resetting of glucose-stimulated insulin secretion to a higher setpoint. The other MODY genes encode transcription factors which have been implicated, principally through studies in genetically modified mice, in beta-cell development and function. For example, in mice null for the *pdx1* gene (the murine homolog of human *IPF1*), there is no pancreatic development, whereas in *pdx-1*$^{+/-}$ mice, and in mice with islet-specific disruption of the gene, the phenotype is one of reduced beta-cell mass and adult diabetes (31,32). Related phenotypes result from disruption of *Neurod* (29) and *Hnf1α* (33–35). Mutations in one of these transcription factors—*HNF1A (TCF1)*—accounts for around two-thirds of all MODY families (21). These distinct molecular aetiologies are associated with substantial differences in clinical course, which help explain the clinical heterogeneity previously noted (22). Heterozygous *GCK* mutations cause fasting hyperglycaemia, present from birth, which is only slowly progressive, usually responsive to diet and leads to few complications. In contrast, *HNF1A* mutations are associated with diabetes onset in early adulthood and a more aggressive and severe deterioration in glucose homeostasis. Individuals with *HNF1A* mutations also show a particular sensitivity to the hypoglycaemic effects of sulfonylureas (36), a clear example of pharmacogenetics in action. As a result of all these factors, it is becoming increasingly important to identify these subtypes in patients presenting with early-onset diabetes, given that a precise molecular diagnosis may offer such patients, and their families, valuable prognostic, diagnostic and therapeutic benefits (20).

What relevance does this information have for multifactorial forms of T2D? Firstly, it is worth noting that most genes in Table 1 exercise their primary effect on insulin secretion rather than action, reinforcing the view, corroborated by studies of intermediate trait heritability (37,38) and rodent knockouts (39), that variation in beta-cell function may well be the predominant factor in influencing T2D risk [an argument developed further by Ashcroft and Rorsman in this issue (40)]. Secondly, demonstration that inactivating *GCK* mutations reduce birth-weight provides proof-of-principle that the relationship between restricted early growth and adult T2D may indeed reflect shared genetic determinants of both (16). Thirdly, there is increasing evidence (see below) that variants in these, and other, genes implicated in monogenic and syndromic forms of diabetes are also directly involved in susceptibility to more common multifactorial forms of the disease.

Table 1. Genes identified as responsible for monogenic and/or syndromic forms of T2D

Gene ID	Alternative gene symbols	Chromosomal location	Gene name	Associated syndrome and notes	Prevalence	Reference (for monogenic/syndromic involvement)	Possible role in multifactorial T2D?	Reference (for multifactorial involvement)
HNF4A	MODY1	20q12–q13.1	Hepatocyte nuclear factor 4-alpha	MODY	+	(26)	+++	(58,59)
GCK	MODY2	7p15–p13	Glucokinase; hexokinase 4	~20% of MODY (heterozygous); permanent neonatal DM (homozygous)	++	(23,24)	++	(63)
TCF1	MODY3, HNF1A	12q22-qter	Hepatocyte nuclear factor 1-alpha; transcription factor 1	~65% of MODY	+++	(25)	+++	(57)
IPF1	MODY4	13q12.1	Insulin promoter factor 1; homeodomain transcription factor	MODY (heterozygous) pancreatic agenesis (homozygous)	+	(28)	+	(62)
TCF2	MODY5, HNF1B	17cen-q21.3	Hepatocyte nuclear factor 1-beta; transcription factor 2	RCAD (renal cysts and diabetes) (=MODY + genitourinary abnormalities)	+	(27)	—	
NEUROD1	MODY6, BETA2	2q32	Neurogenic differentiation1; beta-cell E-box transactivator 2	MODY	+	(29)	—	
LMNA		1q21.2	Lamin A/C	Dunnigans familial partial lipodystrophy; Charcot–Marie Tooth and others	++	(79)	—	
SLC19A2		1q23.3	Thiamine transporter protein, solute carrier family 19 member 2	Thiamine-responsive megaloblastic anaemia (Roger's) syndrome	+	(107–109)	—	
ALMS1		2p13	Alstrom syndrome	Alstrom's syndrome (blindness, deafness, obesity and T2D)	+	(110,111)	—	
PPARG		3p25	Peroxisome proliferator-activated receptor gamma	T2D, insulin resistance with acanthosis nigricans and hypertension	+	(65)	+++	(45–47)
CP		3q23–25	Caeruloplasmin	Aceruloplasminaemia, systemic hemosiderosis	+	(112)	—	
WFS1		4p16.1	Wolframin	Wolfram (DIDMOAD) syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness)	++	(113)	+	(121)
PCSK1	PC1, PC3	5q15–q21	Prohormone convertase 1, prohormone convertase 3, proprotein convertase subtilisn/kexin type 1	Obesity, diabetes, hypogonadotrophic hypogonadism, hypocortisolism	+	(114)	—	
HFE		6p21.3	Haemochromatosis	Haemochromatosis	+++	(115)	+	(122,123)
PLAGL1 and/or HYMAI	ZAC, LOT1	6q24	Pleomorphic adenoma gene-like 1; ZAC tumour suppressor gene; hydatidiform mole associated and imprinted	Transient neonatal diabetes (due to loss of imprinting control)	+	(116)	—	
FRDA		9q13	Frataxin	Friedreich's ataxia	++	(117)	—	
AGPAT2	BSCL1, LPAAB	9q34	1-Acylglycerol-3-phosphate O-acyltransferase-2; lysophosphatidic acid acyltransferase beta	Berardinelli–Seip congenital lipodystrophy	+	(118)	—	
INS		11p15.5	Insulin	Familial hyperproinsulinaemia	+	(64)	++	(55)
BSCL2	GNG2LG	11q13	Seipin; Berardinelli–Seip congenital lipodystrophy 2	Berardinelli–Seip congenital lipodystrophy	+	(119)	—	
INSR		19p13.2	Insulin receptor	Leprechaunism, Donohue syndrome, Rabson–Mendenhall syndrome, insulin resistance syndrome type A	+	(66)	+	(124)
Mt-tRNA Leu(UUR)	Mt3243	Mitochondrial	Mitochondrial tRNA	MELAS (myalgic encephalopathy, lactic acidosis and stroke-like episodes); MIDD (maternally inherited diabetes and deafness)	+++	(120)	+++	(120)

Genes implicated in MODY are listed first, then other genes in chromosomal order. The prevalence of the conditions listed is denoted by the symbols ' +', ' ++', and '+++'. Conditions denoted by '+' are extremely rare (likely to be less than one in a million); those with '+++' are more common, with prevalences as high as one per 1000. The strength of the evidence that common variants in the same genes influence susceptibility to multifactorial type 2 diabetes is also summarized on a semi-quantitative scale, ranging from '—' (no supportive evidence, or gene not yet tested), through '+' and '++' (some supportive evidence) to '+++' (definite involvement). Only representative references are provided.

PROGRESS IN MULTIFACTORIAL FORMS OF THE DISEASE

For most of the hundreds of millions of people with T2D, individual susceptibility to disease is influenced by the conjoint effects of variation at an undetermined number of genomic sites, and the cumulative effect of the various environmental exposures encountered during the individual's life. Progress in susceptibility-gene identification in such circumstances is constrained by a number of factors (41,42). The inherent aetiological complexity of multifactorial diseases means that effect-sizes expected at any individual gene are likely to be modest and to vary between populations, seriously complicating their detection and characterization; and poor understanding of disease biology militates against selection of candidates with strong prior odds for disease involvement (43). These biological limitations have often been exacerbated by sub-optimal study design: the deployment of inadequate sample sizes and failure to take proper account of multiple-testing have been conspicuous and recurrent problems (44).

However, there is increasing optimism that these obstacles are surmountable and, in the past 2–3 years, a growing number of genes demonstrating convincing susceptibility effects have been identified (Table 2). The success of such gene-identification effects is critically dependent on the quality of the genes selected for detailed examination, and these have come from several distinct sources.

Candidate genes arising from biology

Given uncertainties over the pathogenesis of T2D (see above), the list of genes for which it is possible to advance a credible case for involvement in disease susceptibility is large. It includes, but is not limited to, the sets of genes whose products might plausibly be implicated in beta-cell, adipocyte and/or hepatocyte development and function, in insulin-signalling or hypothalamic regulation. Only a small proportion of these will harbour variants that actually have appreciable susceptibility effects (appreciable in the sense of being detectable in reasonably sized data sets). Several hundreds of these biological candidates have been examined for their potential role in T2D. However, few of these studies have been comprehensive in terms of the range of variants studied, or authoritative in terms of the sample sizes examined (41,44). Consequently, few can be considered 'definitive' in terms of proving or refuting an association.

Recent studies, employing larger clinical resources and meta-analyses of published findings, have started to yield more conclusive results. The peroxisomal proliferator-activated receptor gamma (*PPARG*) gene was initially selected for study because of the key role played by PPARG in adipocyte development and function, and as the target of the thiazolidinedione class of insulin-sensitizing drugs. Early studies of a P12A variant in *PPARG* produced inconsistent conclusions, but as larger cohorts were examined and the results combined, evidence accumulated (now exceeding stringent criteria for genome-wide significance) that the proline allele is associated with an ~1.25-fold increased risk of T2D (45–47). As the at-risk allele is present in at least 80% of individuals, this variant generates a population attributable risk for T2D as high as 25%.

Table 2. Common variants with the strongest evidence for a role in susceptibility to multifactorial T2D

Gene ID	Chromosomal location	Gene name	Variants implicated	Odds ratio for T2D	Frequency of at-risk allele in T2D	Notes	References
PPARG	3p25	Peroxisome proliferator-activated receptor gamma	P12A	~1.25	85%	Key regulator of adipocyte development and function	(45–47)
KCNJ11	11p15.1	Potassium inwardly rectifying channel, subfamily J, member 11	E23K	~1.2	40%	Component of the beta-cell K_{ATP} channel	(48–50)
CAPN10	2q37	Calpain 10	SNP43 (CAPN10-g.4852G/A) SNP19 (CAPN10-g.7920indel132bp) SNP63 (CAPN10-g.16378C/T) SNP44 (CAPN10-g.4841T/C)	~1.2	10–25% (SNP44)	Protease of uncertain function implicated in insulin secretion	(83,86)
TCF1 (HNF1A)	12q22-qter	Hepatocyte nuclear factor 1-alpha; transcription factor 1	G319S	~2	~20%	Transcription factor in beta-cell (and other tissues); G319S variant is private to Oji Cree Indians	(57)
HNF4A	20q12–q13.1	Hepatocyte nuclear factor 4-alpha	?	?	?	Transcription factor in beta-cell (and other tissues); association data are so far limited to Finns and Ashkenazim	(58,59)
IRS1	2q36	Insulin receptor substrate 1	G972R	~1.25	~7–10%	Central molecule in insulin signalling cascade	(53)

There has been a similar evolution in understanding of the role of variation in *ABCC8* and *KCNJ11*, neighbouring genes encoding the two components of the beta-cell K$_{ATP}$ channel. This is an essential component of normal glucose-stimulated insulin secretion [see also review by Ashcroft and Rorsman in this issue (40)] and target of the sulfonylurea drugs widely used in T2D to enhance insulin secretion. The earliest studies at this locus generated inconsistent evidence for association at a pair of non-functional variants in *ABCC8* (48). More recently, attention has focused on the E23K variant in *KCNJ11*, for which there has been a steady accumulation of positive evidence (48–50). The susceptibility (K) variant, present in ∼60% of individuals, is associated with a modest odds ratio (∼1.2) for T2D. At present, it remains to be established whether E23K is the sole, or best, marker of T2D-susceptibility at this locus, as substantial linkage disequilibrium extending into *ABCC8* suggests that other variants (in either gene) might contribute to, or underlie, the associations observed. The evidence that the E23K variant has a significant impact on K$_{ATP}$ channel function remains inconclusive (51,52).

Other biological candidates for which there is growing (but, as yet, not incontrovertible) evidence include *IRS1* (encoding insulin receptor substrate 1, a central molecule in insulin-signalling) (53), *GLUT2* (encoding the beta-cell glucose transporter) (54), *INS* (encoding insulin itself) (55) and *PGC1A* (a co-activator of PPARG) (56). However, for each gene, more extensive studies are required before a susceptibility role can be confirmed.

Candidate genes arising from monogenic disease

One of the main motivations behind efforts to map genes for monogenic and syndromic forms of diabetes (particularly MODY) was the belief that variants causing less dramatic disruption of expression and/or function would be found to contribute to more common, multifactorial T2D. Until recently, evidence in support of this belief has been lacking, but recent data are forcing a dramatic reappraisal (Table 1). For example, the G319S variant in *HNF1A* is a major susceptibility gene for T2D in the Oji-Cree Native Canadian population, although it appears to be private to that ethnic group (57). In Ashkenazim and Finnish populations, two recent reports have demonstrated convincing associations with variants adjacent to the *HNF4A* P2 promoter (58,59). Crucially, these variants explain much of the evidence for linkage to chromosome 20 reported in both these populations (60,61). There are some indications that coding variants in *IPF1* increase T2D risk, although the low frequency of these alleles has made it difficult to deliver conclusive proof (62). In addition, there is growing evidence that common variants upstream of *GCK* influence fasting glucose levels (63). Finally, several of the biological candidates implicated in multifactorial disease have rare monogenic or syndromic counterparts (Table 1) (64–66). In retrospect, these findings should come as little surprise. Demonstrating that a gene is responsible for a monogenic form of diabetes provides implicit evidence that there is limited capacity to compensate for dysfunction of that gene through redundancy and/or plasticity. Any other variants in the gene that alter gene expression and/or function are likely to have similar, if less dramatic, phenotypic consequences.

Positional candidates from genome-wide scans

Given the limitations of candidate selection through biology alone, there has been a complementary effort to identify novel pathways involved in T2D pathogenesis through unbiased genome-wide scans for linkage; close to 30 such scans have now been completed in a wide range of ethnic groups (reviewed in 67). The regions of linkage identified in these different scans are far from consistent, indicating that there is no single global linkage signal for T2D akin to that produced by HLA in type 1 diabetes. Differences in study design, family configuration, analytical method and ethnic heterogeneity have undoubtedly contributed to this diversity (67,68). However, as more scans have been completed, some regions have appeared more frequently than expected, and for several of these (chromosomes 1q, 3q, 8p, 10q, 12q and 20 in particular), such replication has prompted the initiation of intensive positional cloning efforts (60,67,69–71). The 1q21–25 region, for example, has been detected in at least eight populations ranging from Pima Indians through Old Order Amish to Chinese (69,72–78), these signals defining a gene-rich region containing many excellent positional candidates—including *LMNA* (encoding lamin A/C, mutations in which can cause lipodystrophy and diabetes) (79) (Table 1) and *IRR* (which codes for the insulin-receptor related receptor thought to play a role in insulin-signalling within the beta-cell) (80). With advances in genotyping technology (81) and a better understanding of linkage disequilibrium patterns in human populations (82), an exhaustive search of this, and other, similar regions for aetiological variants has become feasible.

To date, the only susceptibility gene to emerge from positional cloning efforts in multifactorial diabetes has been *CAPN10* (calpain 10). This gene was identified, following dense linkage-disequilibrium mapping efforts (83), as the strongest statistical candidate within a region of chromosome 2q previously found to be linked to T2D in Mexican-American sibpair families (84). Confirmation—and general acceptance—of these findings has been complicated by several factors. First, evidence for linkage has been limited to Mexican-Americans, though some evidence for association was also evident in Europeans (83,85). Second, the strongest susceptibility effects were observed for particular haplotype configurations involving a trio of intronic variants of uncertain functional impact (83). Third, *CAPN10* encodes a ubiquitously expressed protease with uncharacterized protein targets and few prior biological credentials for involvement in T2D. However, recent studies have started to confirm the biological importance of *CAPN10* variation. A meta-analysis of over 7500 subjects of diverse ethnic origin typed for the 'SNP44' *CAPN10* variant (CAPN10-g.4841T/C), which is in tight LD with a T504A coding polymorphism, indicates a significant overall association with T2D with an odds ratio of ∼1.2, similar to that seen at the *PPARG* and *KCNJ11* loci (86). Pharmacological and biochemical studies of calpain function increasingly point to a role for calpain 10 in insulin secretion (87).

Other routes to gene identification

It is inevitable that other routes to gene identification will contribute additional susceptibility genes in the near future.

A wide range of rodent models of diabetes have being submitted to linkage mapping and positional cloning efforts that should deliver novel susceptibility genes for study in humans (88). One example of such a candidate is *IDE*, encoding insulin-degrading enzyme. This strong biological candidate has been implicated in T2D susceptibility by studies of the Goto–Kakizaki (GK) rat (89) and *Ide*-knockout mouse (90), although analysis of this gene in humans has generated inconsistent findings (91,92).

For most of the past decade, linkage analysis has been the only 'genome-wide' alternative to biological candidate selection for gene-hunters: the limitations of this tool for gene discovery efforts in multifactorial traits are widely accepted. The first attempts to perform genome-wide *association* analyses for T2D have recently been reported (93,94), although the relatively low density of markers employed means these experiments have surveyed only a small proportion of the variation in the genome. As more powerful genomics tools— transcriptional profiling, proteomics and so forth—are applied to the understanding of T2D biology in humans and animal models, revealing genes with strong prior odds for a role in disease pathogenesis (95,96), there is every expectation that this will lead to additional susceptibility variants (43).

LESSONS LEARNED FROM GENETIC STUDIES OF MULTIFACTORIAL T2D

The substantial advances of the past few years provide increasing confidence that additional pieces of the T2D-susceptibility jigsaw will fall into place in the years to come. From those genes so far identified (Table 2), it appears that the effect sizes associated with any individual variant will typically be modest. However, the relatively low power of linkage analysis (97) means that, provided allelic heterogeneity is not extensive, genes revealed by positional cloning efforts within linked regions should have more substantial effects (98).

Reliable detection of such modest associations requires thousands of well-characterized samples (46,48,53,54). Use of case samples enriched for familiality and early onset is a valuable strategy for improving power in initial rounds of gene discovery (98–100), although subsequent studies in large, population-based samples are needed to provide epidemiological context. Even larger sample sizes will be required to characterize these susceptibility genes (for example to distinguish which of several associated variants is most likely to be functional) (101), and to explore gene–gene and gene–environmental effects. In T2D, as in other complex traits, it is increasingly evident that functional variants are not restricted to coding and immediate regulatory regions (55,58,59,83), and that any exhaustive study of a gene must include attention to intronic and remote regulatory regions where those can be defined (102).

The apparent frequency with which genes implicated in monogenic disease reveal themselves to be major players in multifactorial disease is encouraging and provides additional impetus for work in this area. Similarly, the observation that two of the proven susceptibility genes (*KCNJ11, PPARG*) are themselves targets for pharmaceuticals already used in T2D treatment (46,48) supports the concept that the identification of

susceptibility genes active in novel pathways will generate future therapeutic opportunities (103).

As described earlier, genetic information is already playing a part in the clinical care of people with monogenic and syndromic forms of diabetes. The limited predictive value of any of the individual variants so far implicated in susceptibility to multifactorial T2D means that extending molecular diagnosis beyond the monogenic arena remains premature (104). However, as a more complete picture emerges of the inherited component of T2D susceptibility, and the interactions with dietary and other lifestyle exposures, the prognostic, diagnostic and therapeutic value of measuring individual susceptibility will undoubtedly increase (105,106).

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