The genetics of type 2 diabetes and its clinical relevance

Pal A, McCarthy MI. The genetics of type 2 diabetes and its clinical relevance.

The increasing worldwide prevalence of type 2 diabetes (T2D) motivates efforts to use genetics to define key pathways involved in disease predisposition, and thereby to improve management of the disease. Research over the past 5 years has taken the total number of genetic loci implicated in T2D susceptibility beyond 60, and the emphasis is now shifting to the translation of these genetic insights into clinical value. Clinical translation may flow from the identification of novel therapeutic targets, but opportunities also exist with respect to individual prediction, diagnostic biomarkers and therapeutic optimization. To date, the main clinical impact has been seen for relatively rare, monogenic forms of diabetes rather than common T2D. However, the advent of high throughput sequencing approaches may herald discovery of rare and low frequency variants that offer greater translational potential.

Conflict of interest

The authors declare no conflict of interest.

Estimates of future type 2 diabetes (T2D) prevalence are alarming: by 2030, the number of adults diagnosed with T2D worldwide is expected to rise from the current count of 346 million to 552 million (World Health Organization 2011; International Diabetes Federation 2011). This surge in prevalence reflects environmental rather than genetic change (1), but human genetics can still illuminate the mechanisms influencing individual responses to an obesogenic environment, and thereby reveal details about disease pathogenesis that can inform efforts to mitigate the consequences of disease. This review will summarize the principal advances in understanding the genetic basis of T2D, and then consider four aspects of T2D clinical care where genetics has already made, or has the potential for, translational impact.

Genetics of T2D

T2D is a complex, multifactorial trait: both environmental and genetic factors contribute to disease pathogenesis and define individual risk. The relative importance of each almost certainly varies over time and between populations, but estimates of heritability (based on family studies) fall in the region of 30–70%, with strongest heritability observed in patients aged 35–60 years (2).

Human genetics seeks to identify the specific variants that underlie this genetic component of risk. Early efforts focussed on the potential of pedigree-based linkage analysis to uncover highly penetrant alleles that might account for the subset of diabetes which appears to segregate in Mendelian fashion. Collectively, these studies revealed several genes containing rare causal mutations for monogenic forms of diabetes including maturity-onset diabetes of the young (MODY), insulin resistance syndromes and neonatal diabetes (reviewed in refs 3 and 4). Although rare – monogenic forms of diabetes account for, at most, 2% of diabetes – these discoveries provided important clues regarding specific mechanisms of β-cell dysfunction and insulin resistance, and enabled clinically useful genetically based schemas of disease classification that have been of considerable therapeutic and prognostic value (these are discussed further below).

The application of linkage-based methods to common T2D was not particularly fruitful: as now seems clear,
the variants contributing to T2D risk are typically of too modest effect to be detectable using this approach.

The shift towards association studies that followed the seminal paper from Risch and Merikangas (5) was initially directed towards a long list of presumed biological candidates, and did achieve some success. Most particularly, robust associations were observed involving coding variants in the genes coding for two existing therapeutic targets: P12A in peroxisome proliferator activated receptor gamma (PPARG) (6) which encodes the nuclear receptor target of the thiazolidinedione (TZD) class of anti-diabetic drugs (7), and E23K in the potassium inwardly rectifying channel subfamily J member 11 (KCNJ11) that encodes a subunit of the ATP-sensitive K\(^+\) channel which is targeted by sulphonylurea drugs (8). But, in general, few of the candidate genes selected harboured risk variants of large enough effect to be detected in the relatively small sample sizes that were often deployed, whilst at the same time the use of inappropriately liberal significance thresholds led to a profusion of claims of association that proved impossible to replicate.

The recent acceleration in risk-variant discovery in T2D has been catalyzed by the introduction of large-scale genome wide association studies (GWAS). Through systematic interrogation of common variants across the genome, these studies were able to escape the confines imposed by the rudimentary state of our pre-existing knowledge about disease biology. The first round of GWAS in 2007 confirmed known loci at PPARG, KCNJ11 and near TCF7L2 (first identified ahead of the GWAS era by detailed association analysis of a previously demonstrated linkage signal on chromosome 10q (9)), in addition to revealing novel loci including signals near CDKAL1, HHEX, SLC30A8, IGF2BP2 and CDKN2A (10–13). The incremental aggregation of individual GWAS studies into better-powered meta-analyses has driven the total number of common variant signals for T2D over 60 (14–18) (Fig. 1). However, even when combined, these explain no more than 5–10% of disease risk (18, 19).

Whilst these data have provided clues to several aspects of T2D pathogenesis – such as the relationship between T2D, insulin secretion, obesity and insulin resistance (15, 18) – the dividend in terms of precise mechanistic insights has been relatively limited. In large part, this reflects the fact that most of the GWAS signals map to non-coding regions of the genome, and it has proven difficult, despite a variety of approaches (Fig. 2), to establish the functional link to a particular transcript and thereby initiate detailed experimental follow-up. A second factor limiting biological inference and clinical translation has been the modest effect sizes of most identified susceptibility loci (Odds ratio approximately 1.05–1.35) (18, 20).

Much effort is now being put into identifying low frequency and rare causal variants that may have been missed by ‘classical’ GWAS. These may help to improve the proportion of the genetic variance that can be explained (18) and provide access to causal alleles that are more amenable to direct functional investigation [e.g. rare MTNR1B variants, (21)].

Each of the loci identified by discovery genetics provides an opportunity to deliver novel insights into disease pathogenesis and a pathway to clinical translation. The remainder of this review focuses on the current and possible future contribution of T2D genetics in four broad areas of clinical relevance to T2D.

Genetics and disease pathogenesis

New perspectives on known biology

Individuals with T2D have defects in both insulin secretion (suggesting islet dysfunction) and insulin action (resulting in insulin ‘resistance’): the relative contributions of these two processes to T2D pathogenesis has been a matter of sustained debate. The genetic data emerging from GWAS have indicated that most of the common variant T2D signals are driven primarily by the former (18), placing the islet centre stage in terms of T2D development. A minority of identified variants point to constitutive defects involving tissues of insulin action such as fat, muscle and liver (these include the loci near PPARG, KLF14, IRS1 and ADAMTS9) (6, 18, 22) but in the cases of the loci near FTO and MC4R, the effect on insulin resistance is secondary to raised body mass index (BMI) (19, 23, 24).

Another interesting perspective on known biology generated by the GWAS data is that genetic effects on the regulation of ‘normal’ glycaemia (i.e. physiology) and those leading to the dysregulation that occurs in T2D pathogenesis (i.e. pathology) do not appear to be governed by identical mechanisms. This arises from the observation of limited overlap between the genetic variants which affect fasting glucose levels in healthy, non-diabetic individuals and those that are important in the pathophysiological transition to T2D (15, 18, 25, 26). Whilst variants at certain loci (such

**Fig. 1.** Number of T2D susceptibility loci discovered over time divided according to the by ethnic group in whom first identified.
as those near the melatonin receptor *MTNR1B* and the insulin receptor substrate *IRS1* influence both fasting glucose and T2D, others have more specific effects. For example, the T2D-risk alleles at *KCNJ11* and *HNF1A* have no detectable effect on fasting glucose in well-powered studies of healthy individuals, despite the fact that severe mutations in the same genes can lead to highly penetrant forms of early-onset diabetes. Similarly, variants in the glucose-6-phosphatase gene, *G6PC2*, which have relatively strong effects on fasting glucose in healthy subjects, have no impact on T2D risk when examined in large numbers of individuals with T2D and controls (15, 18). These observations to some extent explain why not all individuals with mild fasting hyperglycaemia progress to diabetes (27), and may in the future highlight processes (and biomarkers that can be used for their evaluation) that are of clinical value with regard to risk stratification.

A third area of biology explored by recent genetic studies has been the epidemiological relationship between low birth weight and T2D risk originally described in terms of the foetal origins hypothesis (28). According to this hypothesis, infants who have survived intra-uterine deprivation undergo long-term ‘metabolic programming’ as a result of which they are predisposed to a range of chronic adult diseases, including T2D. A complementary explanation (the so-called ‘foetal insulin hypothesis’) has held that the epidemiological association may reflect the pleiotropic effects of alleles that, through adverse effects on insulin secretion and/or action, result in both reduced intra-uterine growth (insulin being a major trophic factor in foetal life) and enhanced T2D risk (29). The identification of genetic variants influencing these traits has enabled systematic exploration of the validity of the foetal insulin hypothesis. At certain T2D risk alleles, including those near the genes encoding the adenylate cyclase *ADCY5* and the methylthiotransferase *CDKAL1*, there are also strong associations with reduced birth weight (30, 31) which are consistent with the tenets of the foetal insulin hypothesis. Interestingly, at others, such as *TCF7L2*, the associations with birth weight run in the opposite direction with the T2D risk-allele associated with raised birth weight. It has been possible to show that these apparently contradictory effects reflect the competing effects of T2D-risk alleles carried by the foetus (where their tendency is to reduce insulin-mediated growth) and by the mother (where their impact would be an increased risk of gestational hyperglycaemia, resulting in foetal hyperinsulinaemia and accelerated growth). The net effect on infant birth weight will depend on whether the alleles concerned exert a greater effect in early or later life (32).

New biology

The ‘biology agnostic’ approach of GWAS offers the prospect of generating novel insights into T2D pathogenesis, most obviously through the demonstration that a given association signal acts through altered expression or function of a given transcript. The localization of most GWAS signals to non-coding sequence represents an obstacle to inference in this respect, and the most rapid progress has been made when the association signal has been localized to a coding variant, defining the transcript of interest and providing better opportunities for functional validation. An example is the causal coding variant identified in *SLC30A8* which
variants (e.g. in evidence, for example, identifying common genetic exist in T2D (38). However, the more recent genetic insulin-like growth factor 1 (both growth factors) which explained by the high circulating levels of insulin and cancer risk (37). This overlap has previously been observation that anti-diabetes therapies may influence T2D and cancer has also gained recent impetus from the regulation (18). Epidemiological evidence associating T2D-susceptibility loci of genes involved in cell cycle developmental processes, in T2D pathogenesis.

Wnt signalling pathway, recognized for its role in is indeed the cause of the problem, it implicates the as well as beta-cell proliferation (35, 36). If of a number of genes required for insulin secretion expression (34). Furthermore, it has been shown that the TCF7L2 transcription factor, induces expression of a number of genes required for insulin secretion as well as beta-cell proliferation (35, 36). If TCF7L2 is indeed the cause of the problem, it implicates the Wnt signalling pathway, recognized for its role in developmental processes, in T2D pathogenesis.

Finally, one of the most surprising observations to arise from GWAS has been the enrichment within T2D-susceptibility loci of genes involved in cell cycle regulation (18). Epidemiological evidence associating T2D and cancer has also gained recent impetus from the observation that anti-diabetes therapies may influence cancer risk (37). This overlap has previously been explained by the high circulating levels of insulin and insulin-like growth factor 1 (both growth factors) which exist in T2D (38). However, the more recent genetic evidence, for example, identifying common genetic variants (e.g. in HNF1B) which influence both cancer and diabetes in opposite directions (39, 40) suggest alternative mechanisms such as shared components in common signalling pathways. Another explanation for divergent effects on disease risk is an effect on beta-cell proliferation: a risk allele may promote cell cycling and pre-dispose to cancer whilst increasing functional beta-cell mass and reducing T2D risk; conversely if a risk allele effectively reduces cell-cycling it may protect against cancer whilst potentially increasing T2D risk via reduced functional beta-cell mass.

Many of the cell cycle genes in proximity to T2D-susceptibility loci are known to be expressed in islets, raising the possibility that the T2D-predisposing effects of these variants are related to variation in beta-cell mass. The evidence for the ‘cell cycle’ link is most compelling at the chromosome 9p21 association signal (Fig. 3) where the T2D-association signals map in the vicinity of the cyclin dependent kinases (CDKs), CDKN2A and CDKN2B. These are well-recognized tumour suppressor genes: germline CDKN2A mutations are a cause of familial melanoma syndromes and somatic CDKN2A or CDKN2B are amongst the genes most often disrupted by somatic mutations in cancer (41). Rodent data are consistent with a role in glucose homeostasis: overexpression of cdkn2a and knockout of cdk4, a biochemical target of the cyclin-dependent kinase inhibitors encoded by Cdkn2a and cdkn2b, leads to islet hypoplasia and a T2D-like phenotype (42, 43). The mechanism by which the T2D risk variants at chromosome 9p21 (which also harbours an independent association signal for cardiovascular disease) mediate CDKN2A/B expression is as yet unclear but a non-coding RNA, ANRIL (antisense non-coding RNA in INK4 locus: also known as CDKN2B-AS), transcribed close to the region of T2D association, and known to regulate CDKN2B function, is likely to be involved (44–46). One recent study linked the role of another well-known tumour suppressor gene, PTEN, to glucose homeostasis, showing heightened insulin sensitivity (and therefore likely reduced risk of T2D) in PTEN mutation carriers (47).

In summary, T2D genetics has provided profound insights into T2D pathogenesis, refining our understanding of pathophysiology, and implicating novel cellular processes. It is not unreasonable to believe that these advances in our models of disease pathogenesis, will in time, translate into novel therapeutic targets and diagnostic biomarkers, although experience dictates that the timescale over which clinical benefit will accrue runs over decades.

Biology and disease subclassification

One of the desirable clinical outcomes from an improved understanding of disease pathogenesis would be the ability to classify diabetes into subtypes which differ with respect to prognosis and/or management. Such classification is already possible for many of the forms of diabetes that arise in early life, most obviously for the monogenic subtypes of diabetes (Table 1). For example, the different types of MODY vary with respect to age at diagnosis, treatment requirements, progression of hyperglycaemia and disease severity including development of complications. It is now standard clinical practice to seek to establish a molecular diagnosis in individuals suspected of having one of these conditions, and to use this information to guide management.

However, with conventional sequencing at least, the costs of molecular diagnosis are such as to restrict usage to those meeting relatively tight clinical criteria, and, even in the UK, as many as 50% of MODY cases are missed (48). As a result, considerable effort has been
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T2D associated haplotype on Chr 9p21

Impaired regulation/splicing

CDKN2B-AS (ANRIL)

Altered expression CDKN2B

and/or CDKN2A

Fig. 3. Locus plot of the T2D association signal near CDKN2A, and putative functional mechanism

directed towards identifying biomarkers that can allow diagnostic sequencing to be more efficiently deployed. GWAS have contributed here too: the observation that common variants near the HNF1A gene, mutations in which represent the commonest cause of MODY, were associated with C-reactive protein (CRP) levels (49), led to studies which showed that low levels of CRP were characteristic of HNF1A–MODY and could provide useful discrimination against other forms of diabetes presenting in early adulthood (50).

The application of these principles to genetic sub-classification for common forms of T2D is more challenging: most contributing genetic loci are of modest effect with incomplete penetrance and are unlikely, individually at least, to show discriminatory genotype–phenotype correlations equivalent to those seen for the rarer monogenic forms of diabetes. This may not be true for common variants in combination, as the following thought experiment shows. Imagine that the distinction between type 1 and type 2 diabetes was not yet known, and a number of large GWAS have been completed using ‘diabetes’ as the phenotype. Many of the risk alleles now known to be associated with either type 1 (such as HLA) or type 2 (such as TCF7L2) would have eventually been detected in such a study, despite the mix of aetiologies, and would be segregating in both types of cases as well as controls. However, it would have soon become apparent that there was structure to the patterns of association, with risk alleles distributed unequally with respect to age of diagnosis and BMI for example. The next step might be to identify biomarkers (e.g. antibodies to glutamic acid decarboxylase, C-peptide) that were diagnostic of the two disease subtypes.

By analogy therefore, the clinical heterogeneity of common T2D might well, in principle, be hiding subtypes of disease that could be revealed by deeper inspection of GWAS data, and in particular by splitting current aggregated data sets into more homogeneous subsets. The genetic profiles of lean and obese subjects with T2D show some differences (most obviously at loci such as FTO that are primarily associated
### Table 1. Optimal treatments for monogenic diabetes by subtype

<table>
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<tr>
<th>Monogenic diabetes subtype</th>
<th>Distinguishing clinical features</th>
<th>Examples of causal genes</th>
<th>Optimal treatment</th>
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<tr>
<td><strong>Examples of more common subtypes</strong></td>
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<tr>
<td>GCK-MODY</td>
<td>Mild fasting hyperglycaemia</td>
<td>GCK</td>
<td>Diet alone</td>
</tr>
<tr>
<td>HNF1A-MODY</td>
<td>Young onset diabetes</td>
<td>HNF1A</td>
<td>Low dose sulphonylurea</td>
</tr>
<tr>
<td>Neonatal diabetes</td>
<td>Diabetes diagnosed before 6 months</td>
<td>KCNJ11, ABCC8, INS</td>
<td>High dose sulphonylurea, Insulin</td>
</tr>
<tr>
<td>HNF4A-MODY</td>
<td>Young onset diabetes, increased birth weight and macrosomia</td>
<td>HNF4A</td>
<td>Low dose sulphonylurea</td>
</tr>
<tr>
<td><strong>Examples of rarer subtypes with extrapancreatic features</strong></td>
<td></td>
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<tr>
<td>HNF1B-MODY</td>
<td>Renal cysts, genitourinary abnormalities, exocrine pancreatic insufficiency</td>
<td>HNF1B</td>
<td>Early insulin</td>
</tr>
<tr>
<td>Mitochondrial diabetes</td>
<td>Deafness, short stature, pigmentary retinopathy</td>
<td>MTTL1</td>
<td>Sulphonylurea initially but rapid progression to insulin requirement</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>Optic atrophy, diabetes insipidus, deafness, renal tract abnormalities, neurological abnormalities</td>
<td>WFS1</td>
<td>Insulin</td>
</tr>
<tr>
<td>TRMA syndrome</td>
<td>Megaloblastic anaemia, deafness</td>
<td>SLC19A2</td>
<td>Thiamine ± sulphonylurea ± early insulin</td>
</tr>
</tbody>
</table>

GCK, glucokinase; HNF4A, hepatocyte nuclear factor 4A; MODY, maturity-onset diabetes of the young; TRMA, thiamine responsive megaloblastic anaemia.

with BMI, but the distinction is not large enough to guide clinically useful subclassification (18, 51, 52). Ongoing efforts to identify lower frequency variants influencing T2D-risk, some of which may have higher penetrance, may well enable more powerful disease classification, on the basis of individual genetic profile, and/or circulating biomarkers that track those genetic differences (18).

### Disease prevention and risk stratification

The Diabetes Prevention Programme (DPP) and other lifestyle intervention studies have shown that in individuals at high risk for T2D, lifestyle changes can result in a substantial reduction (as high as 58% in the DPP) in medium-term risk of developing T2D (53–56). These studies have also shown that pharmacological intervention in high-risk pre-diabetic individuals can delay or prevent onset of disease (56, 57–59).

There has been considerable interest in determining whether any of the individual variation in response to these interventions can be explained by variation at the known susceptibility loci, not least because such intervention programmes would be extremely difficult to sustain across all pre-diabetic individuals. Both the DPP and the Finnish Diabetes Prevention Study showed that TCF7L2 risk alleles are associated with rates of progression from impaired glucose tolerance to T2D, but these effects were confined to the control groups of both studies, suggesting that the genetic predisposition conferred by the at-risk genotypes could be attenuated by lifestyle changes (60, 61), findings which help to undercut notions of genetic determinism. These data also provide some succour to the notion that it might be possible to use genetic strategies (or non-genetic biomarkers that reflect underlying genetic predisposition) to identify those at highest background risk of T2D conversion. Individuals in these highest risk classes would be most likely motivated to accept, and benefit from, lifestyle and/or pharmacological intervention (62).

Indeed, the prediction of individual risk of T2D remains one of the most prominent anticipated applications of genetic information. The clinical value of current GWAS-identified loci has been investigated by the Framingham Offspring Study (63), the Malmö Preventive Project (MPP) and Botnia Study (64), amongst others (65, 66). Typically, these studies have generated a risk score (essentially a count of the number of risk alleles carried by each individual) and then sought to relate this to individual rates of progression to T2D. These studies have, as expected, confirmed the associations seen in cross-sectional discovery samples, but they have failed to show that the genetic risk score offers any additive discriminative power over existing risk prediction algorithms that are based on traditional clinical risk factors for disease, such as age, BMI and family history. This is, in part, because of the relatively modest effect sizes of the variants identified by GWAS, but it is also likely to reflect the fact that several of those traditional risk factors already encapsulate much of the genetic risk.

In the Framingham and Botnia/Malmö studies, the predictive value of the genetic score has been slightly greater with longer intervals of longitudinal follow-up (64, 67). However, even in this setting, the clinical value of risk score derived from the panel of known GWAS signals remains limited. It is possible that the identification of low-frequency and rare risk variants of larger effect through sequence-based discovery efforts may improve the power of genetic risk
stratification approaches, and/or that it may be possible to harness some of the ‘polygenic’ component to T2D risk that is now evident (68) to similar effect. Whatever the outcome, there will remain significant challenges with respect to the calculation, communication and implementation of risk-score predictions for common complex diseases, particularly in the context of multiethnic populations (69).

Complications and prognosis

The brunt of the morbidity and mortality ensuing from T2D is due to the development of macrovascular and microvascular complications, including diabetic peripheral neuropathy, nephropathy, retinopathy and accelerated cardiovascular disease. Although the progression to such complications is, on the one level, the result of chronically poor glycaemic control, genetic factors are likely to influence individual rates of progression. Diabetic nephropathy, for example, shows some familial aggregation in pedigree studies (70), and individual risk also seems to reflect the burden of parental cardiovascular disease (71).

To date, most of the gene discovery efforts for diabetic complications have been underpowered (reflecting the challenge of compiling well-characterized sample sets of sufficient scale), and reported association findings have replicated poorly. For example, the Genetics of Kidneys in Diabetes (GoKinD) study represents one of the largest sample sets assembled to support GWAS for diabetic nephropathy in T1D (72), although the total case–control data set numbers are, so far, only in the low thousands. Follow-up of findings from the original GWAS (73) has delivered some promising (although perhaps not yet conclusive) replication for regions on chromosomes 11p and 19q33: larger studies are required (74). Systematic meta-analysis of diabetic nephropathy association data provides, at best, only modest support for many of the claims for candidate gene associations (75). One interesting signal has emerged from the uromodulin (UMOD) gene, a urinary protein whose precise function is unclear although there is evidence for a role in renal development (76) as well as in protection against inflammation (77). UMOD variants are associated, at genomewide significant levels, with chronic renal failure (from all causes) (78, 79), an association that seems to extend (albeit at less stringent association) to hypertension (80) and diabetic nephropathy (81).

At the moment, none of these findings has led to clinical translation, but considerable effort is ongoing to extend the scale of GWAS, and to bring next-generation sequencing approaches to bear in the search for low-frequency and rare alleles of greater effect. Identification of genetic factors influencing these conditions would be expected to shed light on the mechanisms driving the development of complications, and offer substantial clinical opportunities, in terms of both novel therapeutic strategies and risk stratification (inviting more stringent blood glucose control in those at greatest risk of the most severe complications).

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Treatment

Discoveries in T2D genetics may impact therapeutic options in two ways. First, if major insights into disease pathogenesis are made, these novel mechanisms may, in time, give rise to new treatments. As one example, the SLC30A8 T2D-risk variant highlights the zinc transporter, ZnT8, as a potential target for pharmaceutical agents (12).

Second, information about an individual’s genome may provide opportunities to optimize therapeutic choice. The clinical use of pharmacogenetics within diabetes is currently limited to monogenic diabetes where a molecular diagnosis clearly informs treatment choice (Table 1). For instance, for patients with diabetes due to HNF1A mutations, sensitivity to the effects of sulphonylureas (82) makes low dose treatment with that class of drugs the first choice; and, for some children with early onset diabetes, a molecular diagnosis of neonatal diabetes due to mutations in KCNJ11 or ABCC8, can enable a safe transfer from insulin injections to oral sulphonylureas (83).

The application of pharmacogenetics within common forms of T2D is of course, more challenging, particularly given any compelling evidence of genotype-driven stratification of disease subtype. Nevertheless, there has been some success in showing that differences in individual response to commonly used oral anti-diabetic agents, at least in part, reflect genetic variation. Most of these studies have focussed on candidate genes selected for their relevance as drug targets, in drug metabolism or in drug transport.

In the case of metformin, for example, variants within the mulidrug and toxin extrusion (MATE) 1 protein encoded by SLC47A1 have been associated with drug response (84–86). More recently, the first GWAS for metformin response showed that variants near ATM (the ataxia telangiectasia mutated gene) were strongly associated with ability to achieve target therapeutic response (a glycosylated haemoglobin level below 7%) (87). Although this study provides some functional support for ATM being the causal gene at this locus [ATM inhibition led to reduced metformin stimulated phosphorylation of AMP-activated protein kinase (AMPK)], others have shown that the insulin sensitizing effects of metformin may be AMPK independent (88) or that, in certain conditions, AMPK can still be activated in the presence of ATM inhibition (89). Whichever gene at this locus is found to be causal, GWAS will have provided a route to novel clues regarding the mechanism of action of metformin, a matter which remains contentious.

Promising results have also been obtained for sulphonylureas, the other mainstays of T2D medication. Individuals carrying two copies of the T2D risk allele at TCF7L2 were twice as likely to show treatment failure in response to sulphonylureas than those homozygous for the non-risk allele (90). There have been similar claims made for the effects of T2D-risk variants at the KCNJ11 and ABCC8 genes, the protein products of which form the components of the sulphonylurea
In the case of the T2D class of anti-diabetic agent, attention has been focussed on variation in PPARγ gene, encoding the nuclear receptor target of TZDs (7), and itself a T2D-risk gene. However, allelic variation at this locus is yet to show consistent association with differential treatment response (94–97).

As things stand, each of these associations is too uncertain, and/or the effects too modest, to merit clinical use at an individual level. However, the data may well be sufficient to define groups at high risk, and this information could prove valuable in designing more efficient clinical trials. Pharmacogenetic studies face formidable challenges, and the future may lie in the integration of several different kinds of study: observational pharmacoepidemiology, genetic studies nested within randomized controlled trials and genotype-based pharmacogenetics (provocative testing of drugs in individuals differentiated by genotype).

Conclusions and next steps . . .

In the last decade, significant progress has been made in diabetes genetics, ranging from the characterization of the genetic basis of many of the rare monogenic forms of diabetes to the identification of many dozens of common variant signals associated with more typical forms of T2D. To date this has had most clinical impact in monogenic diabetes where treatment is guided by a molecular diagnosis. In common T2D, genetics has provided insights into disease pathogenesis from which novel therapies may result. Detailed functional characterization of causal variants as well as the search for low-frequency variants may herald more significant translational potential in the future.

Indeed the search for the ‘missing heritability’ of T2D (given that known loci collectively account for only 10% disease risk) is the matter of much debate. Recent studies suggest that a substantial part may be because of a long tail of additional loci that can be observed in GWAS data (19, 68). Others would argue for a large contribution from low frequency and rare variants (98) especially given recent studies (99) showing the extent of rare and private variation in humans (a result of a rapid explosion in population growth in recent generations). The sequencing studies underway will allow some resolution of this matter, as well as bringing in other types of variant (indels, structural variants) that have been missed to date. In addition, it seems likely that estimates of T2D heritability may have been incorrectly specified perhaps because of epigenetic effects (as a cause of familial aggregation masquerading as heritability) or complex epistatic interactions (100).

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References

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