



# Translating type 2 diabetes genetics: what does it add to clinical practice?

The importance of genetic factors in the aetiology of type 2 diabetes (T2DM) is well established.<sup>1</sup> However, the quest to identify the specific genetic variants associated with increased T2DM risk has been challenging. The initial research approaches included linkage analysis and candidate-gene association studies. Linkage analysis aims to identify genetic loci co-segregating with a specific disease within families and was effective in uncovering the molecular genetic basis of monogenic beta-cell dysfunction (maturity onset diabetes of the young, MODY). This technique also identified the *TCF7L2* gene which has the biggest effect on T2DM susceptibility described to date.<sup>2</sup> Candidate-gene studies examined specific genes postulated to have a role in the pathogenesis of T2DM. Early studies were generally underpowered and, despite massive efforts, these methods initially yielded only two confirmed T2DM susceptibility variants: the Pro12Ala change in the peroxisome proliferator activated receptor gamma (*PPARG*) gene and the E23K polymorphism in the ATP-sensitive potassium channel gene (*KCNJ11*).<sup>3,4</sup> More recently, large-scale association studies confirmed that common variation in the *WSF1* and *HNF1B* genes (in which rare mutations cause Wolfram syndrome and MODY5 respectively) also conferred susceptibility to T2DM.<sup>5,6</sup>

The great breakthrough in late 2007 was the advent of genome-wide association studies (GWAS), which has led to a rapid rise in the number of confirmed susceptibility variants for T2DM.<sup>7-11</sup> These case-control studies are a powerful technique to detect genetic variation predisposing to polygenic diseases by screening the entire genome of individuals with and without the phenotype of interest for a large number of common single nucleotide polymorphisms (SNPs). A higher frequency of a SNP in the cases *versus* the controls suggests that it is associated with the disease, with a p-value of  $5 \times 10^{-8}$  required to satisfy genome-wide significance. GWAS have been facilitated by several recent developments including completion of the Human Genome Project, availability of affordable high-throughput genotyping technologies and multi-centre collections of many thousands of individuals with well-characterised phenotypes. To date, 38 susceptibility loci for T2DM have been identified.<sup>12</sup> Understandably, these landmark findings have stimulated widespread hope that genetic information will provide useful insights into the pathophysiology of this complex disease and ultimately translate into improved care and novel treatments for patients with diabetes.

## Limitations of the GWAS

Although many new and interesting susceptibility loci have been identified, a disappointment has been the small effect size associated with them. The current confirmed susceptibility variants account for only 5–10% of the known T2DM heritability. Therefore significant

research efforts are now being directed to determine the remaining genetic predisposition to T2DM; for example, searching for rare variants with larger effect sizes<sup>13</sup> and small chromosomal structural alterations.<sup>14</sup>

## What genes have been identified?

GWAS allow hypothesis-free global search of the human genome and can therefore identify novel and unsuspected pathways involved in the pathogenesis of T2DM. Most of the T2DM susceptibility variants identified are not close to obvious candidate genes, suggesting that there is much left to be elucidated regarding the pathophysiology of this disease.

However, there are some common themes; the genes implicated are largely involved in beta-cell function and insulin secretion rather than insulin resistance, perhaps surprising given the phenotype of T2DM.<sup>15</sup> This may be due in part to the design of some of the GWAS which matched for body mass index (BMI) and therefore took obesity and insulin resistance out of the equation. The *FTO* gene, predisposing to obesity, was only identified in the UK GWAS, which did not match for BMI.<sup>16</sup> These results do, however, emphasise the crucial role of the beta-cell in all kinds of diabetes.

A further GWAS finding is the potential importance of cell cycle regulation abnormalities in the pathogenesis of T2DM following the identification of several risk loci mapping close to genes involved in this process (such as *CDKN2A/B*). Supporting evidence for the role of cell cycle regulation in beta-cell mass includes islet hypoplasia and development of a T2DM phenotype in rodents with overexpression of *cdkn2a*.<sup>17</sup> Furthermore, GWAS have highlighted that T2DM susceptibility genes have effects on other common diseases including certain cancers.<sup>18</sup> Interestingly, *CDKN2A/B* encode cyclin-dependent kinase inhibitors which are known tumour suppressors.<sup>19</sup> Ongoing research in this area may clarify strong epidemiological data linking diabetes and cancer.

## Applications of the GWAS findings

### Risk prediction

One potential clinical application is the development of personalised susceptibility profiles based on genetic information in order to aid prediction, early detection and prevention of T2DM. This question was addressed by the Whitehall II prospective cohort study in which 20 susceptibility loci associated with T2DM were genotyped in 5535 civil servants (of whom 302 developed new onset T2DM over 10 years).<sup>20</sup> A genetic score based on the number of risk alleles was calculated (maximum score of 40 representing two copies of risk alleles for all 20 variants). This score was compared with two established risk prediction models (Cambridge T2DM risk score and Framingham offspring study T2DM risk score) which incorporate various clinical and biochemical factors such



as BMI, parental history of diabetes and lipid profile. The discriminating power of the phenotype-based risk models was significantly better than the genotype-based risk model in this population. Interestingly, the predictive accuracy of the Framingham offspring study score was not improved by addition of the genetic score. These findings are consistent with similar prospective studies<sup>21–23</sup> which all conclude that traditional risk factors most reliably define risk of developing T2DM, and that there is only minimal improvement by adding currently available genotypic information, although this was higher for younger patients.<sup>21</sup>

The discriminative power of genetic information will increase if more susceptibility loci with stronger effect size are identified and in the future could form the basis of a clinically-relevant risk prediction tool for T2DM. Robust evidence that the use of genotypic information can lead to meaningful changes in human behaviour or allow therapeutic intervention should precede widespread use of genetic testing for prediction. One study reported that a 'high risk' result from genetic testing would motivate the majority of 152 healthy subjects interviewed to adopt healthy lifestyle changes.<sup>24</sup> However, prospective clinical trials would be required to demonstrate that the anticipated enthusiasm would translate into measurable patient outcomes.

### Pharmacogenetics

The glycaemic response and side-effect profile of oral hypoglycaemic medications have marked inter-individual variability. Pharmacogenetics is the effect of genetic variation on therapeutic response and may reflect differences in drug pharmacokinetics or metabolism at a molecular level. Genetic profiling may allow true 'personalisation' of medicine by facilitating optimal treatment choices to maximise clinical efficacy and minimise toxicity. Experience with monogenic diabetes has already demonstrated that genetic information can guide clinical practice and management decisions; for example, individuals with MODY due to heterozygous *HNFI A* mutations are exquisitely sensitive to sulphonylureas.<sup>25</sup> Extending pharmacogenetics to T2DM is more challenging. Initial studies were underpowered and rarely replicated which led to inconclusive and conflicting results. However, some recent studies have demonstrated robust association between genetic variation and therapeutic response. Pearson *et al.* demonstrated that patients homozygous for the diabetes risk allele (G) of the *TCF7L2* variant were twice as likely to fail sulphonylurea (SU) therapy compared with those homozygous for the T allele.<sup>26</sup> A variant in the *ABCC8* gene which encodes the SU receptor (SUR1) has also been shown to affect therapeutic response in a prospective trial of >1000 lean, Chinese T2DM patients treated with gliclazide for eight weeks.<sup>27</sup> Zhou *et al.* showed that those homozygous for the loss-of-function *CYP2C9* alleles were 3.4 times more likely to achieve HbA<sub>1c</sub> targets and had a lower risk of SU failure than wild-type carriers.<sup>28</sup> *CYP2C9* encodes the enzyme cytochrome p450 2C9 which metabolises SUs in the liver, and therefore the reported enhanced SU response could be due to

reduced drug metabolism. Similar studies have been done in metformin-treated patients. Multidrug and toxin extrusion (MATE)1 transporter encoded by the *SLC47A1* gene is responsible for the final step of metformin clearance through bile and urine. Becker *et al.* showed that a variant in *SLC47A1* was associated with reduced HbA<sub>1c</sub> in metformin-treated T2DM patients.<sup>29</sup>

These studies support the proposal that genetic variation can determine response to oral hypoglycaemic agents. Genetic background alone is insufficient to predict response at an individual level, but pharmacogenetics is a developing field with potential to advance the goal of personalised medicine. Future progress will require study of larger cohorts in which drug response is well characterised and eventually, prospective clinical trials to assess whether genotypic information can guide therapeutic choices effectively.

### New therapeutic targets

As well as providing useful insights into the pathophysiology of T2DM, it is likely that the susceptibility loci identified in the GWAS are pointers to biological pathways or molecular targets that may be amenable to therapeutic intervention. The two oldest T2DM susceptibility variants lie within the genes *PPARG* and *KCNJ11* which encode targets of established oral hypoglycaemic agents, thiazolidinediones and sulphonylureas respectively. This highlights that genetic variants of modest effect may illuminate pathways that could be targeted for drug development.

### Summary

Our understanding of the genetics of type 2 diabetes has undergone a revolution in the last three years largely due to the genome-wide association studies. The lack of direct impact on clinical practice to date is not surprising, as these results are still very recent. The identified susceptibility loci are at an early stage of functional characterisation and account for a small proportion of T2DM heritability, which highlights how much work remains to be done in this exciting field. Experience with monogenic diabetes establishes that improved genetic understanding can alter clinical management. The next challenge is to translate the identification of predisposing polymorphisms for T2DM into improved care for patients with diabetes. As clinicians we should be aware of ongoing research efforts and look forward with patient optimism to the clinical repercussions of the current and future genetic discoveries. Clinical benefits are likely to follow on from unsuspected biological insights into the pathogenesis of T2DM. It is also possible that molecular targets for novel therapeutics will be identified and that the vision of 'personalised medicine' – specifically, individualised prediction, prevention and therapy – may eventually be realised.

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**Conflict of interest statement**

There are no conflicts of interest.

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