



DIABETES GENETICS:

tracking, translation & treatment

Dr Richard Elliott, from the Diabetes UK Research Team, speaks to leading UK experts in the genetics of diabetes and reviews progress towards the clinic

The last 10 years have seen striking progress in our understanding of the staggeringly complex genetics of Type 1 and Type 2 diabetes (the most common forms of the condition) and that of rarer forms caused by changes in individual genes (monogenic diabetes). Much remains to be learnt, but genetic studies are beginning to uncover the otherwise hidden mechanisms behind each type of diabetes, which suggest they are far more diverse than current broad definitions would indicate.

I reviewed advances towards the clinic and spoke to leading experts, Andrew Hattersley (Professor of Molecular Medicine at University of Exeter Medical School and Consultant Physician at Royal Devon and Exeter NHS Foundation Trust) and Mark McCarthy (Robert Turner Professor of Diabetic Medicine at the Oxford Centre for Diabetes, Endocrinology and Metabolism and Group Head at the Wellcome Trust Centre for Human Genetics).

Genetics & diabetes risk

Although more than 85 per cent of Type 1 diabetes occurs in individuals with no previous family history, among common health problems it is one of the most heritable – with risk increasing for those who have close relatives living with the condition. Risk rises from 0.4 per cent (in those without a family history) to 2–4 per cent (in people with an affected mother), 6–9 per cent (in people with an affected father), 10 per cent (in people with an affected sibling), 10–19 per cent (affected non-identical twin), up to 30 per cent (both parents affected) and 30–70 per cent (affected identical twin). Similarly, people who have Type 2 diabetes in the family are two to three times more likely to develop the condition than people who don't. We know that genetic changes linked to Type 1 and Type 2 usually regulate the expression of a gene, rather than changing or blocking its function directly, and many physiological and developmental pathways are thought to be involved.

"The hope was that the genetics would point to a small number of specific

processes as the cause of diabetes," says Prof McCarthy. "But we now know that's not the case." Early genetics studies have enabled the identification of DNA regions linked to a greater risk of the conditions. And from 2007 onwards, genome-wide association studies, followed by improvements in high-throughput technology for gene sequencing, have helped scientists to look at millions of common genetic changes in larger and larger populations and find out which of them occur more often in people with diabetes.

There are more than 50 genetic regions linked to Type 1 diabetes. As an autoimmune condition, changes to genes of the human leukocyte antigen (HLA), which code for cell-surface proteins that control the immune system, are by far the strongest genetic risk factors. Studies of HLA genetics in Type 1 have been going on for over 40 years, but evidence shows that non-HLA regions are also involved, the most important of which is the insulin gene, supporting the idea that genetic changes linked to Type 1 diabetes also affect islet cells.

In Type 2 diabetes, there are now over 100 genetic regions linked to increased risk although, unlike HLA in Type 1 diabetes, it is clear that there is no single region of overwhelming importance. Most of the regions involved in Type 2 diabetes risk seem to act by influencing the development or function of the pancreatic islets, while others alter the sensitivity of liver, fat and muscle to the insulin they produce. For example, changes close to the TCF7L2 gene (which controls the function of islets) provide the strongest genetic risk factors for Type 2 diabetes, in Europeans and also impact on patients' response to treatment with sulphonylureas. However, these effects are too modest to provide powerful prediction of Type 2 risk or response to



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treatment on an individual level, and have therefore not yet had significant clinical impact.

While concrete evidence to support it is lacking, the 'thrifty genotype' hypothesis suggests that the current Type 2 epidemic might be linked to genetic selection that has favoured individuals who are more efficient at storing and preserving energy when food supplies are uncertain – leading to higher rates of obesity when high-calorie foods are plentiful. Potential 'thrifty genes', such as those in the FTO region, (which encodes a protein that modifies DNA) are linked to higher levels of body fat and the risk of obesity which, in turn, also increases the risk of Type 2.

As with other debates over the influence of nature versus nurture, the idea that people develop diabetes because of their genetics alone is oversimplistic. Instead, our risk of diabetes is a mix of our genetic inheritance, early life factors related to our environment in the womb and environmental triggers (such as viral infection in Type 1 diabetes and weight gain in Type 2 diabetes). Also involved are epigenetic factors (changes, such as DNA methylation, which regulate the expression and function of genes) and shifting patterns of interaction between different genes and between genes and the environment. For example, the 'metabolic memory' hypothesis ▶



suggests that changes in glucose levels can cause modifications in DNA structure that are memorised within cells long after those changes have occurred. Genetic factors are also thought to play a role in the differences in Type 2 diabetes risk between South Asians and Europeans. But further genetic studies are needed to find out if unique Type 2 diabetes genes exist within these populations. “It’s really quite complex,” says Prof McCarthy, “and quite hard to detect exactly what mix of factors is to blame.”

Despite the progress of genetics research, known genetic factors exert only a modest influence on the risk of Type 1 and Type 2 diabetes. Indeed, scientists are only able to explain 80 per cent of the genetic contribution towards Type 1, and less than 15 per cent of the contribution towards Type 2 – the tip of a genetic iceberg still waiting to be uncovered.

From the lab to the clinic

So far, improvements in the clinical management of diabetes as a result of genetic discoveries have been restricted to the rarer, monogenic forms of the condition. In contrast to Type 1 and Type 2 diabetes, the genetic changes that lead to monogenic forms have much more dramatic and predictable consequences – typically, severe defects in the function of insulin-producing beta cells. Identifying the subtypes of these

forms based on their genetics now allows us to identify patients who are more likely to respond to particular therapies and then tailor their treatment accordingly. To date this is the best example of the application of pharmacogenetics to diabetes.

Neonatal diabetes is one of the most severe forms of diabetes but, thankfully, also one of the rarest. It is almost always diagnosed within the first six months of life. Patients with the most common cause (a change in the beta cell potassium channel) have the ability to sense changes in blood glucose and the ability to produce insulin, but the connection between these systems is missing, so that no insulin is released. Treatment of the condition has been transformed by work at the University of Exeter, which revealed that patients with this particular genetic change can get excellent diabetes control with high dose sulphonylurea treatment in 90 per cent of cases. As a result, patients can now be diagnosed using genetic tests and switched from lifelong insulin therapy to oral sulphonylureas (usually glibenclamide), leading to dramatic improvements in quality of life that have made national news headlines.

“It is still very exciting thing for the Exeter team when we hear feedback from parents who have been getting up two or three times a night to check their child’s blood glucose levels and can just stop all that,” says Prof Hattersley. “The main problem is now just making sure

that everyone diagnosed before the age of six months is able to access a genetic test.” His team now offers the test for free to anyone diagnosed with diabetes before the age of six months, anywhere in the world and have already received almost 1,500 samples from patients in 85 different countries.

Maturity Onset Diabetes of the Young

The other form of monogenic diabetes, Maturity Onset Diabetes of the Young (MODY) runs in families, is typically diagnosed before the age of 25 and accounts for around 1–2 per cent of diabetes cases. The most common forms involve changes in the genes for glucokinase (involved in the sensing of glucose) and HNF-1 alpha (a transcription factor that turns genes on and off).

Patients with glucokinase MODY have stable glucose levels only slightly higher than those of people without diabetes and carry a very low risk of diabetes complications. Medical treatment is unnecessary and does not lower the regulated glucose. “Although we know that one in a thousand people in the UK population have it, we’ve only found it in a tiny fraction of those people,” says Prof Hattersley. “It’s surprisingly common, but we’re not rushing to find these patients because this form of diabetes is only a problem when doctors prescribe treatment. It’s really a case of trying to rescue people from doctors! These patients have good glucose control – but that’s in spite of treatment, rather than because of it!”

Cases of HNF-1 alpha MODY are

more severe and patients are at risk of complications. Patients also tend to be slim and often get misdiagnosed with Type 1 diabetes and treated with insulin for years – even though they respond more favourably to sulphonylureas. To help identify MODY patients and target their treatment more effectively, Prof Hattersley led work to develop new genetic tests and integrated them into care pathways.

As a result, as many as 15,000 patients around the world now have a better quality of life. “In some ways the genetic research was the easy bit,” says Prof Hattersley. “The difficulty now is getting diagnosis into clinical practice. We’re pursuing a combined approach of education and training to help improve the number of diagnoses that are made.”

To this end, the University of Exeter now trains Genetic Diabetes Nurses from all over the country, so that they can learn about monogenic diabetes and become local experts who provide education and patient support in their region. They also offer an online MODY probability calculator that lets any clinician take simple characteristics and ask how likely that patient is to have MODY. “That’s had over 11,500 visits to date – and it’s better than me! We’ve done a head-to-head test, with me against the MODY calculator, and the calculator won because it takes into account all of the information and integrates it. Every year, we also hold a practical Monogenic Diabetes Symposium for nurses and doctors that is about making the correct diagnosis and getting the treatment right.

Looking to the future

Ultimately, research on monogenic diabetes shows that having a better understanding of why someone develops diabetes can help to improve the choice of treatment. The same principle is also likely to apply in Type 1 and Type 2 diabetes, albeit indirectly and on a longer timescale.

“While research into genetic changes that increase the risk of Type 1 and Type 2 diabetes is providing insights into the biology of these conditions, it’s unlikely

that genetic data on the most common forms of diabetes will be of direct use in the clinic,” argues Prof Hattersley.

“If you think of the human genetic code as a library, with each gene as a single book, the causes of monogenic diabetes would be like badly misspelled words in one of those books. In contrast, the genetic causes of Type 1 and Type 2 diabetes are merely American spellings. Individually they don’t cause a problem, but lots of them in lots of different books can eventually cause problems. Even if the science improves, data on those kinds of changes won’t be directly useful in the clinic because they simply aren’t predictive enough.”

Owing to the weaker influence of individual genetic markers and the role of environmental factors in Type 1 and Type 2 diabetes, for these conditions genetics is only half the story. Noting someone’s family history of diabetes and other characteristics (such as their age and body mass index) already help accurately predict their risk of diabetes without genetic tests. Therefore, genetic information is likely to be most useful in improving our biological understanding to help us to find new, more targeted therapies and better ways of using them to help patients.

“In Type 2 diabetes, several of the genetic signals that we’ve found map onto genes that are already targeted by treatments such as thiazolidinediones and sulphonylureas,” says Prof McCarthy. “We believe that many other genetic signals point towards other novel targets that, with a bit of luck, can be converted into new ways of treatment and prevention.”

At the moment, we have only a simple diagnosis of Type 1, Type 2 or monogenic diabetes, although we know there is more variation in people’s diabetes. The hope is that genetics will help us work out why. Prof McCarthy believes that we should be able to place people on a map that shows the contribution of different factors to their diabetes. Maybe, given their position on the map, we can work out the best treatment for them.

“It’s going to be quite a long road but we’ve already seen vast improvements,” he adds. “Not just in the technology of genetics research but in the way in which groups of researchers are working together to tackle what is a huge problem that none of us could tackle alone. I think it will be a gradual process, but I would hope that we will see more and more use of research information in the clinic in the years ahead. In 20 years’ time, it’s likely that we will all have had our genomes sequenced and the information posted in our medical records, giving us some clues to an individual’s risk of diabetes. If we can combine that with better ways of measuring our environmental history and possibly markers in the blood that track the early development of diabetes, we will have made major strides in bringing diabetes under control.”

i Further information about monogenic diabetes, Genetic Diabetes Nurses and the University of Exeter’s MODY probability calculator and Monogenic Diabetes Symposium 2016 are available at www.diabetesgenes.org

FURTHER READING

- 1 McCarthy M (2015). Genomic medicine at the heart of diabetes management. *Diabetologia* April 10 [Epub ahead of print]
- 2 Rubio-Cabezas O, Hattersley A, Njolstad P et al (2014). The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatric Diabetes* 15 (Suppl. 20); 47–64
- 3 Shields BM, Hicks S, Shepherd MH et al (2010). Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia*, 53 (12); 2504–2508
- 4 Todd JA (2010). Etiology of Type 1 diabetes. *Immunity* 32 (4); 457–467