Genetics is fundamentally changing the way in which biologists classify the world. Genetic studies are, for example, revealing numerous cryptic species that look the same (phenotype), but that are genetically distinct. One genetic study, for example, resolved the neotropical skipper butterfly *Astraptes fulgerator*, first described scientifically in 1775, into at least 10 species in north-west Costa Rica alone.¹

Genetic studies are also revealing ‘cryptic diseases’ that look the same clinically (phenotype), but that are genetically distinct, show varying trajectories and may need different therapeutic approaches. For example, genetic sequencing raises the prospect of targeting cancer therapies to each tumour’s specific mutational profile. Indeed, the genetic variability that underlies, for example, breast cancer is starting to “direct the appropriate treatment to the appropriate patient at the appropriate time” – so-called ‘precision medicine’.²

More recently, genetic analysis helped delineate five subtypes of ‘adult-onset diabetes’ (see Table 1), which might represent “a first step towards precision medicine in diabetes”.³

“Precision diabetes treatment comes a step closer” ~ MARK GREENER

The recently published *Lancet Diabetes and Endocrinology* paper that identifies five subtypes of adult-onset diabetes associated with differing risk of complications has sparked new debate on the classification of diabetes and may help bring precision medicine a step closer.

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“This paper has helped to start a vital conversation about how we categorise types of diabetes. With more than 3.6 million people diagnosed with diabetes in the UK, we hope to move away from the perhaps simplistic approach of using just two main types of diabetes, recognising the many different charac-
A heterogeneous disease

The presentation and progression of type 2 diabetes is highly heterogeneous. After all, numerous biological pathways, arising from a variety of interactions between genes and environmental factors, cause the progressive loss of β-cell mass, function or both that results in diabetes. Despite their different origins, the pathways end at a common destination: hyperglycaemia. According to Leif Groop, Senior Professor in Endocrinology at Lund University and Research Director at Helsinki University, who led the new study, this heterogeneity might help explain why, despite current treatments, diabetes often progresses and why so many patients develop complications.

Indeed, differentiating the various types of diabetes clinically can be difficult. For example, fewer than 10% of people with diabetes have latent autoimmune diabetes in adults (LADA), caused by auto-antibodies against glutamic acid decarboxylase, the enzyme responsible for synthesising gamma-aminobutyric acid (GABA). Best known as an inhibitory neurotransmitter in the brain, islet beta-cells also produce GABA, which regulates their function. At diagnosis, LADA is clinically indistinguishable from type 2 diabetes. Over time, however, LADA increasingly resembles type 1 diabetes.

Moreover, a growing number of studies suggest that early and intensive control of hyperglycaemia produces a persistent reduction in the risk of diabetic micro- and macrovascular complications, even if HbA1c levels are similar over the longer term or healthcare professionals subsequently intensify treatment. Several biological changes — including oxidative stress, non-enzymatic glyca- tion of proteins, epigenetic changes and chronic inflammation — seem to lay the foundation for this “metabolic memory.” Currently, however, healthcare professionals cannot predict at diagnosis which patients need intensified treatment.

Five clusters

Against this background, Professor Groop’s team analysed 8980 patients with newly diagnosed diabetes enrolled in the Swedish All New Diabetics in Scania (ANDIS) registry. They then used statistical techniques to see how complications and medication use clustered around six variables: age at diagnosis; body mass index (BMI); HbA1c; homoeostatic model assessment (HOMA2) estimates of beta-cell function and insulin resistance; and whether or not the patient expressed glutamic acid decarboxylase autoantibodies.

The authors selected the variables by assuming that diabetes emerges when patients cannot increase insulin secretion sufficiently to meet the greater metabolic demands associated with obesity and insulin resistance. In addition, they chose variables for which the information was easily available, with the minimum number of laboratory tests.

In ANDIS, 1.5% of adults had type 1 diabetes, 5.3% had LADA and 1.2% had secondary diabetes arising from co-existing pancreatic disease. Missing data meant that the researchers could not classify 3.8% of patients. The remaining 88.3% of patients had type 2 diabetes. The analysis revealed five replicable clusters, characterised by significantly different patient characteristics and risk of diabetic complications (see Table 1). For instance, the cluster ‘severe autoimmune diabetes’ (SAID) overlapped with type 1 diabetes and LADA. The authors say that another two clusters — ‘severe insulin-deficient diabetes’ (SIDD) and ‘severe insulin-resistant diabetes’ (SIRD) — “represent two new, severe forms of diabetes previously masked within type 2 diabetes.” “The clusters resonate very well with our clinical experience of managing people with diabetes,” Professor Groop comments.

The authors then compared disease progression, treatment and development of diabetic complications, which revealed some marked differences. For example, SAID and SIDD had substantially higher HbA1c at diagnosis (80.0 and 101.9mmol/mol [9.5% and 11.5%] respectively) than the other clusters (eg 50.1mmol/mol [6.7%] in the cluster ‘mild age-related diabetes’ [MARD]) and the difference persisted throughout follow-up. SAID and SIDD also showed the highest rates of ketoacidosis at diagnosis (31% and 25% respectively compared to less than 5% in the other clusters).

### Table 1. Characteristics of the five clusters of adult-onset diabetes based on the Swedish All New Diabetics in Scania (ANDIS) analysis

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Prevalence</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe autoimmune diabetes (SAID)</td>
<td>6.4%</td>
<td>Early-onset, relatively low BMI, poor metabolic control, insulin deficiency, glutamic acid decarboxylase antibody positive</td>
</tr>
<tr>
<td>Severe insulin-deficient diabetes (SIDD)</td>
<td>17.5%</td>
<td>Early onset, relatively low BMI, low insulin secretion (low HOMA2-B index), poor metabolic control, glutamic acid decarboxylase antibody negative</td>
</tr>
<tr>
<td>Severe insulin-resistant diabetes (SIRD)</td>
<td>15.3%</td>
<td>Insulin resistance (high HOMA2-IR index), high BMI</td>
</tr>
<tr>
<td>Mild obesity-related diabetes (MOD)</td>
<td>21.6%</td>
<td>Obesity, no insulin resistance</td>
</tr>
<tr>
<td>Mild age-related diabetes (MARD)</td>
<td>39.1%</td>
<td>Older than the other clusters, modest metabolic abnormalities</td>
</tr>
</tbody>
</table>
HbA1c strongly predicted ketoacidosis at diagnosis (odds ratio [OR] 2.73 for each standard deviation change). SIRD and the final cluster ‘mild obesity-related diabetes’ (MOD) showed the highest prevalence of non-alcoholic fatty liver disease (24.1% and 21.9% respectively). Zinc transporter-8 – a protein that moves this essential mineral into cells – is another autoantigen that the immune system targets in some people with type 1 diabetes. Autoantibodies against zinc transporter-8 were seen mainly in patients with SAID (27.3% compared with <2% in other clusters).

Treatment patterns also differed between some clusters. For example, 41.9% and 29.1% of patients with SAID and SIDD respectively received insulin therapy, compared with less than 4% of patients in the other clusters. The proportion of patients on metformin was highest in patients with SIDD (77.8%) and lowest in SAID (44.7%). But metformin use was just 48.8% in SIRD, which, the authors suggest, is the group expected to benefit the most from this drug. They suggest that the “traditional classification is unable to tailor treatment to the underlying pathogenic defects”.

The clusters may also offer prognostic insights. For example, early signs of diabetic retinopathy (mean duration 135 days) were more common in SIDD than in the other clusters (eg OR 1.6 compared with MARD). In particular, the risk of developing chronic kidney disease (CKD) differs between clusters. SIRD patients had the highest risk of developing CKD. During a mean follow-up of 3.9 years, 22.3% of the SIRD group reached stage 3a CKD (estimated glomerular filtration rate [eGFR] <60ml/min/1.73m²). After adjusting for age and sex, CKD risk was more than doubled in SIRD patients compared with MARD patients (hazard ratio [HR] 2.41). Moreover, 8.8% and 1.9% SIRD patients reached stage 3b CKD (eGFR <45ml/min/1.73m²) and end-stage renal disease respectively: about three and five times higher than for MARD (HR 3.34 and 4.98 respectively).

The authors suggest that the increased risk of CKD in SIRD patients reinforces the association between insulin resistance and renal disease. Indeed, the relatively low HbA1c levels may suggest “that glucose-lowering therapy is not the optimum way of preventing this complication”.

Finally, the researchers analysed genetic loci (regions of chromosomes) that previous studies associated with diabetes and related traits. “Genetic studies support the five aetiologically distinct subgroups of adult diabetes,” Professor Groop says. Indeed, the genetic associations in the clusters differed from those in traditional type 2 diabetes.

No genetic variant was associated with all clusters. But several cluster-specific associations emerged. For example, a variant of the TCF7L2 gene (rs7903146), which encodes a transcription factor (a DNA sequence that turns certain genes on and off) previously associated with type 2 diabetes, was also associated with SIDD, MOD and MARD, but not SIRD. The rs10401969 variant in the TM6SF2 gene, previously linked to non-alcoholic fatty liver disease, was associated with SIRD but not MOD. This pattern suggests that SIRD is characterised by a particularly unhealthy form of obesity – in other words, as part of the metabolic syndrome – compared with MOD. Adding other biomarkers, genotypes or genetic risk scores may help further refine the model.

**Further studies**

Despite the strong associations, the study authors say that they “cannot at this stage claim that the new clusters represent different aetiologies of diabetes, nor that this clustering is the optimal classification of diabetes subtypes”. Future studies also need to determine whether patients can move between clusters, and hone the model by exploring other autoantibodies and additional complications, including blood pressure and blood lipids.

The researchers replicated the findings using patients enrolled in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844) and Diabetes Registry Vaasa (n=3485). However, only 15.1–26.6% of those in the various registries were not of Scandinavian origin. So further studies need to assess the approach in people from other ethnic backgrounds. “Since performing the initial analysis, we have replicated the results in UK and Dutch cohorts,” Professor Groop reports.

The clustering also suggests that randomised trials should target insulin secretion in SIDD and insulin resistance in SIRD. “Our study suggests that clinicians could consider intensive treatment, which might mean insulin, from the beginning in people with SIDD,” Professor Groop explains. “In SIRD, we should try to enhance insulin sensitivity. We may not, however, have any drugs that enhance insulin sensitivity sufficiently, although pioglitazone might be one option. For MOD and MARD, we can offer lifestyle advice, use metformin and patients can enjoy life without fear of complications. In addition, using the most appropriate treatment means that society can save money.”

The researchers are developing a web-based tool to assign patients to specific clusters. “It will be an app for the clinic, telling clinicians which subgroup the patient probably suffers from, which treatment would be best, and the possible problems and side-effects,” Professor Groop says.

**Implications for clinical practice**

“While the results are important, we are some distance from any new classification reaching routine clinical practice,” Dr Burns remarks. “The conversation this study has started is a real strength. It’s very important that we think beyond type 1 and type 2 diabetes if we’re to develop more personalised ways to prevent, diagnose and treat these conditions. The clusters highlight differences between people with type 2 diabetes and, therefore, the importance of moving beyond this one-size-fits-all diagnosis in the future.

“However, the clusters in this paper aren’t fully representative of individuals in a clinic – there is likely to be a great deal of variation, with other features not looked at in this research being important,” Dr Burns concludes. “Although there is a great deal of research currently underway to help us reach this goal, we’re a long way from having clear
definitions and definitive subtypes for type 1 or type 2 diabetes that can help to guide clinical practice. When we do, it could lead to a much more tailored and targeted approach to diabetes care."

References

Declaration of interests
Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He also receives royalties from two books aimed at the general public about diabetes. He has no shares or financial interests.

Mark Greener is a freelance medical writer