The many faces of diabetes: addressing heterogeneity of a complex disease

Diabetes is a group of chronic metabolic disorders that share the common feature of hyperglycaemia, meaning that, in principle, diabetes can be diagnosed via measurement of a single blood component. However, elevations in blood glucose can be caused by a number of genetic and acquired factors that reduce the circulating concentrations of insulin or decrease its effectiveness, leading to heterogeneity in the clinical presentation and progression of the disease.1 Although existing classifications for diabetes provide archetypes based on reasonably pure pathogenetic mechanisms,1 an important goal of clinical and genetic research in adult-onset type 2 diabetes is to identify more refined subtypes to accurately predict clinical outcomes and identify targeted therapies that ameliorate them.

In The Lancet Diabetes & Endocrinology, Emma Ahlqvist and colleagues2 used unsupervised clustering methods to create a data-driven classification for patients with diabetes. They selected six parameters that could be measured in a single clinic visit and were reasonably unaffected by therapy, including age at diagnosis, BMI, glutamate decarboxylase antibodies (GADA; to identify patients with autoimmune diabetes), HbA1c (to assess blood glucose control), homoeostatic model assessment 2 (HOMA2)-B (to assess β-cell function based on C-peptide concentration), and HOMA2-IR (to assess insulin resistance). Using data from 8980 individuals in the All New Diabetics in Scania cohort, a longitudinal cohort that aims to enrol and obtain baseline metabolic phenotypes from all patients with newly diagnosed diabetes in the Scania region of Sweden, they identified five clusters of patients who could be distinguished at the onset of their disease and who showed different clinical trajectories in terms of initiation of therapy and development of complications. The first cluster (labelled as severe autoimmune diabetes [SAID]) included 577 (6%) of the 8930 clustered patients and was genetically associated with the rs2854275 variant in the HLA locus (odds ratio [OR] 2·05, 95% CI 1·69–2·56; p<0·0001). Patients in this cluster were GADA positive and had a mean age at diagnosis of 50·5 years (SD 17·9). The second cluster (severe insulin-deficient diabetes [SIDD]) included GADA-negative patients, had the lowest HOMA2-B score of all the clusters, and showed no association with rs2854275.

Despite the difference in GADA status, patients with SAID shared many common features with patients with SIDD, including low BMI, insulin deficiency, high HbA1c concentration at diagnosis, initial treatment with metformin, and poorer control when treated. Patients in clusters 4 and 5 had relatively milder and better-controlled diabetes than patients with SAID or SIDD, developed renal and vascular complications at a slower rate, and were characterised by obesity (cluster 4; mild obesity-related diabetes) or increased age at diagnosis (cluster 5; mild age-related diabetes). The clusters were replicated in three other Scandinavian cohorts, which showed similar clinical trajectories to the first cohort.

The group’s primary goal was to stratify patients with diabetes at the time of diagnosis to identify those at risk of developing severe disease. In this aim they succeeded, identifying a cluster of patients with severe insulin-resistant diabetes (SIRD; cluster 3). These patients had a mean age of 65·3 years (SD 9·3) at diagnosis, with higher HOMA2-B and HOMA2-IR scores (reflecting incomplete β-cell compensation for insulin resistance) and decreasing C-peptide concentrations over 8 years of follow-up (by contrast with the stable concentrations seen in the other clusters). Although treatment led to better control in patients with SIRD than in patients with SAID or SIDD, patients with SIRD were more likely to develop end-stage renal disease and coronary events. Unlike other GADA-negative clusters, cluster 3 showed genetic association with rs10401969 (a variant in TM6SF2; OR 0·62, 95% CI 0·52–0·75; p<0·0001), but not with rs7903146 (located in TCF7L2, a well-established type 2 diabetes risk locus;4 1·00, 0·87–1·15; p=0·86), despite adequate study power. At a time when genetic studies5 are increasingly supporting a major role of β cells in diabetes susceptibility, the increased prevalence of severe complications in insulin-resistant patients with higher HOMA2-B scores revisits the longstanding controversy around the role of insulin resistance in diabetes pathogenesis.6

In providing information about disease prognosis, Ahlqvist and colleagues extend earlier studies that
used combinations of genetic risk scores, clustering, and regression analysis to identify subtypes of type 2 diabetes on the basis of clinical and genetic parameters. These include studies that identified distinct subtypes associated with insulin sensitivity, processing, and secretion;\textsuperscript{7} that showed that the heterogeneous effects of obesity on type 2 diabetes risk could be explained by individual subcutaneous adipose storage capacity;\textsuperscript{1} and that identified a subgroup of patients with type 2 diabetes whose clinical features mimicked a mild form of lipodystrophy.\textsuperscript{9} The study also complements a large-scale topological analysis\textsuperscript{10} of health records and genotyping data that identified three subgroups of patients with type 2 diabetes who showed differences in development of microvascular, macrovascular, malignant, neurological, and immune comorbidities.

In interpreting these results, it is important to consider the effects of age on the prevalence of end-organ damage, particularly for patients with SIRD. In future studies, it will be crucial to investigate whether the classification assigned to an individual patient changes as they age. It is also important to recognise that the study was done in reasonably homogeneous Scandinavian populations, and that the generalisability of the results might be limited by genetic or environmental risk factors and by a model based on C-peptide concentration, which is not commonly measured in the clinic. Nevertheless, the finding that simple parameters assessed at the time of diagnosis could reliably stratify patients with diabetes according to prognosis is compelling and poses the challenge of development of methods to predict outcomes of patients with type 2 diabetes that are more generalisable and comprehensive. Additionally, the physiological basis of the features characterising each cluster provides a strong rationale to investigate the genetic architecture and molecular mechanisms that lead to heterogeneity in the presentation and progression of diabetes in adults.

Rob Sladek  
McGill University and Génome Québec Innovation Centre, Montréal, Québec H3A 0G1, Canada; and Department of Human Genetics and Department of Medicine, McGill University, Montréal, Québec, Canada  
rob.sladek@mcgill.ca

I declare no competing interests.
