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Genetics and neonatal diabetes: towards precision medicine

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Diabetes is a lifelong chronic disease. During the past 100 years, its diagnosis has been based on measurements of raised blood glucose concentrations. In the 1960s, diabetes was subclassified based on age at onset and need for insulin treatment (ie, juvenile or maturity onset; insulin or non-insulin-requiring diabetes). Because diabetes was believed to be an inherited disease, much hope was placed on the identification of genetic markers that would help to diagnose diabetic subgroups. Although investigators in the 1970s noted that type 1 diabetes was strongly associated with the HLA locus on chromosome 6, determination of HLA genotypes did not add substantial diagnostic value because of their high prevalence.[1] The discovery of autoantibodies to different islet antigens in the 1980s[2] added strong discriminatory power to the diagnosis of autoimmune type 1 diabetes, and this knowledge was later applied to a late-onset autoimmune form of diabetes in adults.[3]

The first real genetic breakthroughs in diabetes classification came with the discovery that mutations in the genes encoding glucokinase, *HNF1A,* and *HNF4A* were associated with different forms of maturity-onset diabetes of the young.[4–6] Whereas maturity-onset diabetes of the young can show varying penetrance and severity, neonatal diabetes, a rare (1:100 000 births) severe form of diabetes, is diagnosed in infants younger than 6 months. The group in Exeter, UK, pioneered the genetic dissection of neonatal diabetes, and noted that one form could be linked to mutations in the *KCNJ11* gene encoding the Kir6.2 subunit of the ATP-dependent potassium channel in pancreatic islets, and could be treated with sulfonylureas.[7,8] During the past 20 years, more than 20 genes have been identified as causing neonatal diabetes, as discussed by Elisa De Franco and colleagues in their accompanying study in *The Lancet*.[9]

In many of these monogenic diseases, a causal diagnosis has had an important effect on choice of treatment and disease outcome. In one striking case,[10] after identification of a mutation in the *KCNJ11* gene in a poorly developing child with neonatal diabetes and switching from insulin to large doses of sulfonylurea, the child's diabetes could not only be well controlled, but development, walking, and talking became possible. Kir6.2 is also expressed in the brain, and this combination of diabetes, developmental brain defects, and sometimes epilepsy has been called developmental delay-epilepsy-neonatal diabetes. Clear evidence exists of a genetic diagnosis improving treatment.[7,8]

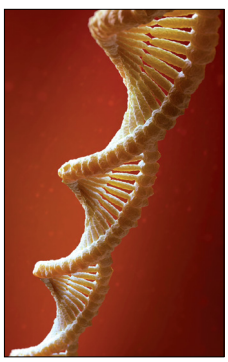
In patients diagnosed with maturity-onset diabetes of the young, those with mutations in the glucokinase gene do not need any treatment because the mutation only modestly raises the threshold for the phosphorylating capacity of the enzyme, but the slight increase in glucose can fully overcome this defect. Therefore, maturity-onset diabetes of the young 2 caused by glucokinase mutations

is not really a disease, but a compensated metabolic disorder.[11] One of my patients received a diagnosis of diabetes as a child, but, after many years and about 19 000 insulin injections, received a precise genetic diagnosis that her diabetes was caused by a mutation in the glucokinase gene. Now, she needs no treatment.

The Exeter group has not only pioneered research in this specialty, but also removed barriers by providing genetic tests to patients from many different countries for free covered by research grants.[8] In the early days of the study in 2000, genetic testing was expensive and time consuming, and the investigators used Sanger sequencing of genes that were selected on the basis of previous clinical information. The addition of targeted next-generation sequencing to Sanger sequencing in 2012 reduced the cost and time required, and also broadened the range of variants that could be tested without clinical data. This change resulted in the identification of a genetic diagnosis in 82% (840/1020) of tested patients in De Franco and colleagues' study.[9] Because most patients are now referred within weeks of being diagnosed with diabetes, physicians can achieve an early genetic diagnosis and predict the development of associated clinical features. Indeed, De Franco and colleagues document the clinical benefit of early diagnosis and treatment in certain subgroups of patients with neonatal diabetes.[9]

This approach still requires a prediction of the genes to sequence, which is reasonable in neonatal diabetes (ie, with a clear phenotype of diagnosis of diabetes <6 months of age), but not all cases of monogenic diabetes are this clear cut. The next step in less clear clinical situations will be whole-genome sequencing without any assumptions about what genes might be involved. Although cost is a restriction in this situation, this whole-genome sequencing approach can already work for recessive mutations, which are rare.

We recently identified three recessive mutations in *BBS10* causing the Bardet-Bield syndrome in an analysis of next-generation sequence data from Finland.[12] The three adult carriers had not been diagnosed with the syndrome, even though clinical features meant that Bardet-Bield syndrome could not be excluded. However, many challenges will need to be overcome before whole-genome sequencing becomes part of routine clinical work-up in different specialties. Hopefully the UK Government's 100 000 Genome Project and the US$215 million promised by President Obama to create a Precision Medicine Initiative in the USA will provide impetus towards this goal. Such projects should not only lead to more precise diagnosis informing treatment in different genetically-determined diseases, but also increase the number of affected individuals who will benefit from diagnosis and treatment.



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For the **100 000 Genome Project** see www.genomicsengland.co.uk

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