Milestone 11

The discovery of monogenic diabetes

The genetics of diabetes was a highly debated topic in the 1970s (Milestone 3) and studies proposed many possible modes of inheritance. Early reports from Tattersall provided evidence for the genetic heterogeneity of diabetes. He described the presence of a form of non-insulin-dependent diabetes, known as maturity-onset diabetes of the young (MODY), characterized by early onset (<25 years of age) and an autosomal-dominant mode of inheritance. The molecular basis underlying glucose intolerance in MODY remained unknown for many years.

In 1992, laying the groundwork for future studies, Froguel and colleagues performed genetic linkage analysis in 16 French families who displayed clinical characteristics of MODY to map and identify the genes causing their diabetes. The researchers investigated candidate genes involved in glucose transport, such as *SLC2A2* (encoding GLUT2), *GCK* (encoding glucokinase, the key enzyme in glucose metabolism) and a candidate region (adenosine deaminase, *ADA*) on the long arm of chromosome 20 that co-segregated with MODY.

In this first study, 14 of the families showed significant genetic linkage between the *GCK* locus on chromosome 7p and diabetes. Different families also showed varying linkage to *ADA*, highlighting the heterogeneity of MODY. Subsequently, two independent teams in France (Froguel and colleagues) and in the UK (Hattersley, Turner et al.) reported that mutations in *GCK* were the cause of hyperglycaemia in a large proportion of French and UK MODY families.

In 1996, in two seminal studies, Yamagata and colleagues used linkage analysis and identified that mutations in *HNF1A* and *HNF4A* (encoding transcription factors originally described in the liver) resulted in severe progressive insulin secretory defects and hyperglycaemia associated with microvascular complications. These studies represent a landmark in the field, as they shed light on the importance of transcription factors for pancreas development and function. Furthermore, patients with this genetic aetiology were shown to respond optimally to oral sulfonylureas, providing an early example of precision medicine.

Adding to the repertoire of monogenic diabetes, in the mid-2000s, different groups investigated the cause of another form of monogenic diabetes, which presents in the first 6 months of life, called neonatal diabetes. Gloyn and colleagues discovered that heterozygous activating mutations in *KCNJ11* (encoding ATP-sensitive potassium channel subunit Kir6.2) were the major cause. Certain *KCNJ11* mutations may also be associated with developmental delay, muscle weakness and epilepsy. Furthermore, moderately activating mutations in *KCNJ11* caused transient neonatal diabetes, highlighting the multiple phenotypes associated with this gene. Subsequent studies identified *ABCC8* (encoding sulfonylurea receptor) and *INS* (encoding insulin) as additional genetic causes. With the advances in molecular genetics, MODY-related mutations have been identified in different genes, including *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *INS*, *NEUROD1*, *PDX1*, *ABCC8*, *KCNJ11*, *CEL* and *RFX6*.

A correct diagnosis of MODY or neonatal diabetes can have profound implications for treatment and prognosis. Importantly, studies focusing on the clinical care of patients with MODY reported that the aetiology of hyperglycaemia affected the treatment outcomes. For instance, sulfonylurea therapy was found to be safe and more effective than insulin therapy in patients with *KCNJ11* mutations and future studies also confirmed its long-term efficacy and safety.

"the knowledge of monogenic diabetes has evolved from simple clinical characteristics to well-defined molecular genetics"

Since the 1970s, the knowledge of monogenic diabetes has evolved from simple clinical characteristics to well-defined molecular genetics. Despite such advances, >80% of patients are not diagnosed via genetic testing, probably owing to costs and unavailability of tests in certain settings. The field has moved towards next-generation sequencing, which provides a highly sensitive method for simultaneous analysis of all monogenic diabetes genes. Precision medicine has taken momentum; a systematic approach integrating advances in biology and technology and implementing universal screening programmes in a cost-effective manner is imperative to achieve the best possible outcomes for all patients.

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Milestone studies

Froguel, P. et al. Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus. *Nature* **356**, 162–164 (1992) | Hattersley, A. T. et al. Linkage of type 2 diabetes to the glucokinase gene. *Lancet* **339**, 1307–1310 (1992)

Further reading

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