Monogenic forms of diabetes mellitus: an update

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There are several monogenic disorders of pancreatic β-cell function, characterized by various degrees of chronic hyperglycemia. They are usually diagnosed early in life, in neonates or during infancy, in childhood and even in young adulthood1,3. The identification of causal mutations in a dozen of different genes has already proven to have a great clinical impact opening new avenues in genomic medicine and pharmacogenetics4,5. These diseases comprise a broad spectrum of diabetic phenotypes including neonatal diabetes mellitus, non-autoimmune diabetes in infancy, dominantly inherited forms of early-onset diabetes (also named Maturity-Onset Diabetes of the Young [MODY], and first recognised by Tattersall in 1975) and very rare diabetes-associated syndromes1-3,6.

Both Neonatal Diabetes Mellitus (NDM) and Monogenic Diabietes of Infancy (MDI, as diabetes may be silent in the first couple of months of life) are rare (∼1:300,000 live births) but potentially devastating diseases as causing low, or even undetectable levels of insulin2,3. Two forms are recognized on clinical grounds, either transient (TNDM) or permanent (PNDM), which differ in the duration of insulin dependence early in the disease, and to some extent in their genetic and molecular origins2,3 (fig. 1). In most instances, early-infancy diabetes is unrelated to auto-immunity3. NDM/MDI are indeed genetically heterogeneous disorders mainly caused by heterozygous mutations in \(\text{KCNJ11}\), \(\text{ABCC8}\) and \(\text{INS}\) genes7-10. Rarer genetic aetiologies which may include extra-pancreatic features have been reported, including recessive mutations in \(\text{IPF1}\) (causing pancreas agenesis and exocrine pancreatic insufficiency), \(\text{PTF1A}\) (in association with cerebellar hypoplasia), \(\text{GLIS3}\) (in association with congenital hypothyroidism) and in \(\text{EIF2AK3}\) (causing Wolcott Rallison syndrome)1,3.

The MODY subtype, a group of clinically heterogeneous, often non-insulin-dependent forms of diabetes, usually develops in childhood or in thin young adults (before age 25 years) and may represent 1-2% of all diabetes cases1,6. So far, heterozygous mutations or chromosome rearrangements in seven genes have been identified as responsible for MODY (fig. 2). These genes encode the enzyme glucokinase (\(\text{GCK}\), MODY2), the transcription factors hepatocyte nuclear factor-4α (\(\text{HNF4A}\), MODY1), hepatocyte nuclear factor-1α (\(\text{HNF1A}\), MODY3), insulin promoter factor-1 (\(\text{IPF1}\), MODY4), hepatocyte nuclear factor-1β (\(\text{HNF1B}\), MODY5)

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and NEUROD1/beta2 (MODY6), and the preproinsulin (INS, MODY7)1,6,11,12.

The most recent discoveries within the last 5 years, with important clinical and therapeutic implications, are:

– The activating mutations in the β-cell K_ATP channel. This channel is a hetero-octamer assembled from the pore-forming K_6.2 (KCNJ11) subunit and the regulatory, high affinity sulfonilurea receptor SUR1 (ABCC8)13, which links nutrient metabolism with membrane electrical activity by responding to changes in ATP/ADP levels that reflect the energy status of the β-cell13. Therefore, it plays a key role in the regulation of insulin release. These gain-of-function KCNJ11 or ABCC8 mutations are indeed responsible for 30-to-40% of the NDM cases7,9. Heterogeneity in the symptoms associated with the K_ATP channel mutations has been reported, notably neuromotor and neuropsychological abnormalities with distinctive degrees of severity may be present4,5,7. Moreover, some ABCC8 mutations resulted in vertical transmission of neonatal and apparent adult-onset diabetes in the same family7, or rare forms of insulin secretion deficiency in adults14.

The most striking clinical implication of these studies is the radical change in the treatment of the patients with a K_ATP channel mutation. A switch from insulin therapy to oral sulfonilurea drugs (glibenclamide or glipizide) provides a good metabolic control in both PNDM and relapsing TNDM cases with separate KCNJ11 or ABCC8 mutations4,5,7.

– The heterozygous mutations in the preproinsulin (INS) gene are also a cause of isolated permanent NDM/MDI, accounting for 15-20% of permanent MDI. The age of diabetes onset ranges from the neonatal period through childhood and adulthood8,10,15. One common feature in patients with an INS mutation is the absence of autoantibodies8,10,15, clinically implying that children with autoantibody-negative diabetes diagnosed in the first years should be investigated for monogenic diabetes (instead of being considered type 1 diabetes). As demonstrated in the dia-

![Fig. 1. Distribution of the genetic subtypes in Neonatal Diabetes Mellitus/Monogenic Diabetes of Infancy (NDM/MDI). Data from the French NDM Study group5,7,8. GCK: glucokinase; INS: preproinsulin.](image)

![Fig. 2. Distribution of the genetic subtypes in Maturity Onset diabetes of the Young (MODY). Overall data from two representative cohorts of patients (British and French MODY cohorts), adapted from previous reports6,9. HNF: hepatocyte nuclear factor; INS: preproinsulin; IPF: insulin promoter factor.](image)

**Distribution of the MODY subtypes**

<table>
<thead>
<tr>
<th>Transcription factors</th>
<th>British</th>
<th>French</th>
<th>MODY-X</th>
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<tbody>
<tr>
<td>Glucokinase (GCK)</td>
<td>30-60%</td>
<td>2-5%</td>
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</tr>
<tr>
<td>HNF1α</td>
<td>1-3%</td>
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<td>&lt; 1%</td>
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<td>HNF4α</td>
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<tr>
<td>MODY2</td>
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<tr>
<td>(TCF1/ (HNF4A/ (TCF2/ (PDX1/ Beta2)</td>
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<tr>
<td>MODY3) MODY1) MODY5) MODY4) (MODY6)</td>
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![Endocrinol Nutr. 2009;56(Supl 4):26-9 27](image)
betic Akita mouse, INS mutants causing NDM/MDI were found to promote proinsulin misfolding, endoplasmic reticulum stress and β-cell failure supporting a proteotoxic, apoptotic mechanism. These data still expand the pathogenic mechanisms of β-cell dysfunction in NDM/MDI, and evidence the potential phenotypic heterogeneity of these rare forms of non auto-immune diabetes.

Altogether, the discovery of genes that are highly expressed in the pancreatic β-cell and involved in these monogenic subtypes of diabetes has revealed several aetiological mechanisms of β-cell dysfunction in NDM/MDI, and evidence the potential phenotypic heterogeneity of these rare forms of non auto-immune diabetes.

The recent discoveries in the field of NDM/MDI, in addition to the previous studies in MODY, strongly support the hypothesis that different mutations affecting a same gene may cause a wide spectrum of clinical phenotypes ranging from NDM to inherited diabetes with a lower penetrance appearing in childhood or adulthood. Furthermore, there is rising evidence that common polymorphisms in the genes previously implicated in monogenic diabetes can modestly increase the risk for common adult type 2 diabetes (such as GCK and HNF4A promoter variants, intronic variants in HNF1B, or coding and non coding variants in WFS1/Wolfram syndrome gene).
Identifying the precise genetic causes and molecular mechanisms that explain the clinical features of each subtype of early-infancy or childhood diabetes has significant implications in: a) our molecular understanding of these monogenic β-cell disorders; b) how these discoveries may be translated to novel pharmacogenomic approaches to improve diabetes care in these subgroups of very young patients, and c) a better prediction of disease progression and useful genetic counselling.

Conflict of interest

The authors declare they have no conflict of interest.

REFERENCES