Abstract

Maturity onset diabetes of the young (MODY) is a genetically and clinically heterogeneous subtype of non-insulin-dependent diabetes mellitus (NIDDM) characterised by early onset, autosomal dominant inheritance and a primary defect in insulin secretion. To date, three MODY genes have been identified on chromosomes 20q (MODY1/hepatic nuclear factor 4a), 7p (MODY2/glucokinase) and 12q (MODY3/HNF-1α). Mutations in MODY2/glucokinase result in mild chronic hyperglycaemia as a result of reduced pancreatic beta-cell responsiveness to glucose, and decreased net accumulation of hepatic glycogen and increased hepatic gluconeogenesis after meals. In contrast, MODY1 and MODY3 are characterised by severe insulin secretory defects, and by major hyperglycaemia associated with microvascular complications. The role of the three known MODY genes in susceptibility to the more common late-onset NIDDM remain uncertain. Genetic studies seem to exclude a role as major susceptibility genes, but leave unresolved whether they may have a minor role in a polygenic context or an important role in particular populations.

MODY is a monogenic form of NIDDM

It is now recognised that non-insulin-dependent diabetes mellitus (NIDDM) is a genetically, metabolically and clinically heterogeneous syndrome of multifactorial aetiology (1). Although, in most cases, NIDDM seems to be a polygenic disorder, several monogenic forms have also been identified (2–5). Among those monogenic forms, maturity onset diabetes of the young (MODY) has been the most intensively investigated in the past few years, and a large body of data is now available on its genetic and pathophysiological mechanisms (6). MODY is characterised by familial NIDDM with an early age of onset (childhood, adolescence or young adulthood) and autosomal dominant inheritance, associated with defects of insulin secretion. The well-defined mode of inheritance, with high penetrance, and the early age of onset of the diabetes, which allows the collection of multigenerational pedigrees, made MODY an attractive model for genetic studies of NIDDM. The variable phenotype of subjects with MODY suggested that the disorder was genetically heterogeneous, an observation that was confirmed by genetic studies (Table 1). Mutations in genes on chromosomes 20q, 7p and 12q, designated MODY1/hepatic nuclear factor 4a (HNF-4a) (7, 8), MODY2/glucokinase (GCK) (5, 9, 10) and MODY3/HNF-1α (11, 12) respectively, can cause this form of diabetes. Moreover, there are likely to be additional MODY genes, as there are families in whom MODY does not co-segregate with markers tightly linked to the three known MODY loci (11), and no mutations are found in the known genes (13).

The prevalence of MODY remains unknown, but it seems to have a world-wide distribution (10, 14). Although it is commonly believed to be a relatively rare form of NIDDM, its frequency might have been underestimated, as the associated hyperglycaemia can remain undiagnosed until adulthood. Recent studies suggest that 2–5% of patients with NIDDM may in fact have MODY (15), and MODY was found in approximately 10% of the white families with NIDDM we have studied in France (5). The relative prevalences of the different MODY subtypes remain uncertain. Analyses of a set of 67 MODY families that we have now identified in France show that 63% (42 families) have the MODY2 and 21% (14 families) have the MODY3 subtypes (10, 13, 16). Thus the additional unknown MODY locus or loci represent 16% of the families in our group. In contrast, Frayling et al. (17) have observed that MODY2/GCK mutations represent only 11% of cases of MODY in a group of British kindreds, whereas HNF-1α mutations are highly prevalent (73%) in that population. These
contrasting results may be due to differences in the genetic background of the two populations, or they may reflect, at least partly, ascertainment bias in the recruitment of families.

Glucokinase and MODY

Glucokinase phosphorylates glucose to glucose-6-phosphate in pancreatic beta-cells and hepatocytes, and has a major role in the regulation and integration of glucose metabolism (18). More than 80 different GCK mutations have been observed to date (10, 19). Expression studies have shown that the enzymatic activity of the mutant proteins was impaired, with a decrease in $V_{\text{max}}$ or a decrease of the affinity of the enzyme for glucose (20). Impairment in the enzymatic activity of mutant GCK results in decreased glycolytic flux in pancreatic beta-cells (21). This defect translates in vivo as a glucose-sensing defect, leading to an increase in the blood glucose threshold that triggers insulin secretion (22), and a rightward shift in the dose–response curve of glucose-induced insulin secretion (23). Comparison of insulin secretion rates in the presence of different concentrations of glucose demonstrated that those who are glucokinase deficient present an average 60% reduction in insulin secretion for a given glucose concentration. Interestingly, subjects carrying mutations that affect only mildly the enzymatic activity of glucokinase in vitro present a much lower reduction in insulin secretion rates compared with controls than do subjects carrying severe mutations. The release of insulin in response to arginine is usually well preserved (24), which suggests that this secretory defect is indeed related to glucose sensing.

Decreased net accumulation of hepatic glycogen (Fig. 1) and augmented hepatic gluconeogenesis after meals were observed in glucokinase-deficient patients (25). Because most of the glucose that is taken up by the liver after a meal is converted to hepatic glycogen (26), any decrease in net hepatic glycogen synthesis is expected to exacerbate postprandial hyperglycaemia. Normal glucose tolerance after a meal also depends on normal suppression of hepatic glucose production (27). In this regard, the increased rate of gluconeogenesis observed after a meal is also likely to be an important contributing factor to postprandial hyperglycaemia in glucokinase-deficient persons. In support of this, we have observed abnormal suppression of hepatic glucose production by physiological concentrations of insulin during an euglycaemic clamp (28). In addition, Tappy et al. (29) have shown that glucokinase-deficient patients have decreased hepatic glucose cycling, and an endogenous glucose production that is abnormally high in relation to their plasma glucose concentrations, and that they present a blunted suppression after oral administration of glucose. These results suggest that, in addition to the altered beta-cell function, abnormalities in liver glucose metabolism play an important part in
the pathogenesis of hyperglycaemia in patients with MODY2. In this regard, attenuation of pancreatic and hepatic glucokinase expression in transgenic mice results in pancreatic and hepatic defects comparable to those observed in GCK-deficient subjects (30–32).

Despite these multiple defects in the pancreas and the liver, the hyperglycaemia associated with GCK mutations is often mild, with fewer than 50% of subjects presenting overt diabetes (10). However, it develops during the early years of life (youngest age at diagnosis, 12 months) and its penetrance in the affected families is very rapidly complete, in that the individuals who carry the mutation are nearly always affected before puberty (10). In glucokinase-deficient subjects, we found no evidence for the well-established association of NIDDM or impaired glucose tolerance with a cluster of risk factors for macrovascular disease including hypertension, obesity and dyslipidaemia, which is consistent with the low frequency of coronary heart disease in these patients. Despite the long duration of hyperglycaemia, glucokinase deficiency is not associated with an increased frequency of late complications of diabetes. We have observed a lower prevalence of proliferative retinopathy, proteinuria and peripheral neuropathy in MODY2 than in other subtypes of MODY and late-onset NIDDM (10, 33). This may be a consequence of the relatively small increase in blood glucose concentrations and of the low prevalence of hypertension in these patients.

**MODY3 (HNF-1α) and MODY1 (HNF-4α)**

MODY3 was recently identified as the gene encoding HNF-1α (12), a transcription factor involved in tissue-specific regulation of liver genes, but also expressed in pancreatic islets and other tissues (34). More than 50 different mutations in HNF-1α were found to co-segregate with NIDDM in MODY families of various populations (12, 13, 16, 17, 35–38). An insulin-secretory defect in the absence of insulin resistance was observed in diabetic and non-diabetic carriers of MODY3 mutations (39, 40), suggesting that HNF-1α is indeed implicated in pancreatic beta-cell function. However, the mechanisms and the target genes associated with this beta-cell defect remain unknown.

Regarding the clinical presentation of diabetes, we have recently compared data from subjects with MODY2, MODY3 and late age of onset NIDDM (33). The clinical phenotype of MODY3 resembles late age of onset NIDDM in its natural history, with patients progressing rapidly from impaired glucose tolerance to overt diabetes, and with deterioration of insulin secretion. In contrast to the usually mild hyperglycaemia resulting from glucokinase deficiency, MODY3 is a severe form of diabetes, often evolving to insulin requirement. Proliferative retinopathy has been observed as frequently in patients with MODY3 as in those with late age of onset NIDDM (Table 2). When adjusted for the duration of the diabetes, the odds ratio to develop retinopathy was intermediate in patients with MODY3 compared with that in GCK-deficient patients (in whom it was threefold lower) and those with late age of onset NIDDM (in whom it was 2.6-fold higher). A trend towards a higher prevalence of proteinuria in patients with MODY3 was also observed. However, unlike NIDDM with late age of onset, the MODY3 subtype is associated with a low prevalence of obesity, dyslipidaemia and arterial hypertension. Moreover, unlike MODY2, MODY3 is not a disease of childhood, with hyperglycaemia usually developing after puberty.

MODY1 seems to be much less prevalent than the other subtypes of MODY. The American RW pedigree, comprising 360 identified members, including 72 known affected subjects, was, until recently, the only family found to show linkage with the MODY1 locus (7). Following the identification of MODY3 as the transcription factor HNF-1α (12), MODY1 was identified as
Mellitus (NIDDM). Values are expressed as mean ± S.D.

Table 2 Retinopathy and proteinuria in patients with maturity onset diabetes of the young (MODY) and non-insulin-dependent diabetes mellitus (NIDDM). Values are expressed as mean ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>MODY3</th>
<th>GCK</th>
<th>Other MODY</th>
<th>NIDDM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>24</td>
<td>65</td>
<td>12</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Sex: M/F</td>
<td>8/16</td>
<td>27/38</td>
<td>6/6</td>
<td>71/79</td>
<td>0.58</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 ± 18*</td>
<td>46 ± 17*</td>
<td>49 ± 21*</td>
<td>62 ± 12</td>
<td>0.0001</td>
</tr>
<tr>
<td>Duration of known hyperglycaemia (years)</td>
<td>23 ± 13</td>
<td>19 ± 11</td>
<td>18 ± 6</td>
<td>17 ± 9</td>
<td>0.06</td>
</tr>
<tr>
<td>Fasting glucose concentration (mmol/l)</td>
<td>8.9 ± 2.6</td>
<td>7.2 ± 1.5*</td>
<td>6.4 ± 1.2*</td>
<td>9.7 ± 3.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prevalence of proliferative retinopathy (n (%))</td>
<td>5 (21%)</td>
<td>2 (3%)</td>
<td>1 (8%)</td>
<td>34 (23%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Odds ratio (95% confidence interval)a</td>
<td>–</td>
<td>0.27 (0.08–0.92)b</td>
<td>–</td>
<td>2.69 (1.27–5.74)c</td>
<td></td>
</tr>
</tbody>
</table>

Proteinuria

<table>
<thead>
<tr>
<th></th>
<th>MODY3</th>
<th>GCK</th>
<th>Other MODY</th>
<th>NIDDM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>26</td>
<td>78</td>
<td>12</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>Sex: M/F</td>
<td>11/15</td>
<td>38/40</td>
<td>57</td>
<td>86/80</td>
<td>0.45</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 ± 17*</td>
<td>45 ± 19*</td>
<td>53 ± 13</td>
<td>63 ± 12</td>
<td>0.0001</td>
</tr>
<tr>
<td>Duration of known hyperglycaemia (years)</td>
<td>22 ± 13</td>
<td>18 ± 10</td>
<td>19 ± 5</td>
<td>18 ± 9</td>
<td>0.20</td>
</tr>
<tr>
<td>Fasting glucose concentration (mmol/l)</td>
<td>8.7 ± 2.8</td>
<td>7.1 ± 0.9*</td>
<td>6.5 ± 1.4*</td>
<td>9.9 ± 3.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129 ± 11*</td>
<td>127 ± 17*</td>
<td>133 ± 18</td>
<td>140 ± 15</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 7</td>
<td>74 ± 9*</td>
<td>70 ± 12*</td>
<td>80 ± 10</td>
<td>0.0001</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>84 ± 28</td>
<td>84 ± 21</td>
<td>75 ± 17</td>
<td>86 ± 25</td>
<td>0.55</td>
</tr>
<tr>
<td>Prevalence of proteinuria (n (%))</td>
<td>5 (19%)</td>
<td>4 (5%)</td>
<td>0 (0%)</td>
<td>11 (7%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Statistics are contingency-table χ² test (qualitative traits) and ANOVA (quantitative traits).
a Statistically significant differences (P < 0.05) compared with NIDDM (Tukey–Kramer HSD test following ANOVA).
b Odds ratio compared with MODY3 subjects; c P = 0.03; d P=0.009.
(Data adapted from reference 33, with permission).

the gene encoding HNF-4α (8), a member of the steroid/thyroid hormone receptor superfamily and upstream regulator of HNF-1α expression. A nonsense mutation (Q268X) resulting in a truncated protein was found to co-segregate with MODY in the RW pedigree (8). The affected individuals from that pedigree also present a severe form of diabetes that requires insulin therapy in about 30% of cases and is associated with microvascular complications (41). A primary pancreatic beta-cell defect was observed in these patients (42, 43). Recently, a second mutation in the HNF-4α gene has been identified in a British pedigree with MODY (44).

**MODY genes and late onset NIDDM**

Insulin resistance is a risk factor for the development of late onset subtypes of NIDDM (45). However, the full expression of diabetes also requires defective or deficient beta-cell function. For obvious reasons, the MODY genes were considered as strong candidate genes for the insulin secretory defect of late onset NIDDM. The GCK gene was intensively investigated in several populations. Positive associations between diabetes and markers on chromosome 12q in the region of MODY3 were observed when all families from the cohort were tested together, without stratification by the insulin secretory status. It is possible that MODY3 and this NIDDM locus represent different genes on chromosome 12q. Alternatively, they may represent different alleles of a single gene. Several common amino acid polymorphisms have been observed in the HNF-1α gene and, although their allele frequencies do not seem to be different in NIDDM subjects compared with those in the general population (12, 53), it is possible that these polymorphisms may have a physiological or pathophysiological role in beta-cell function. Thus an amino acid polymorphism on regions upstream of the promoter have a drastic effect on transcription (48). The hypothesis that some forms of diabetes might be associated with mutation in these regulatory regions is supported by the co-segregation of a variant of the pancreatic promoter region with late age of onset NIDDM, observed in one French family (47). Furthermore, it was demonstrated recently that this variant was associated with reduced beta-cell function in Japanese-American subjects with normal or impaired glucose tolerance, and that this defect progressed during a 5-year follow-up (49). This mutant allele could contribute to a high risk of abnormal glucose tolerance in this population.

Linkage of the MODY3 locus with late onset NIDDM was excluded in a panel of 600 white French sib-pairs (50), but was observed in 53 white American sib-pairs (51). Moreover, genetic linkage has been reported between diabetes and markers on chromosome 12q in the region of MODY3 in a small cohort of Finnish families characterised by late onset NIDDM with defective insulin secretion (52). In that study, no linkage was observed when all families from the cohort were tested together, without stratification by the insulin secretory status. It is possible that MODY3 and this NIDDM locus represent different genes on chromosome 12q. Alternatively, they may represent different alleles of a single gene. Several common amino acid polymorphisms have been observed in the HNF-1α gene and, although their allele frequencies do not seem to be different in NIDDM subjects compared with those in the general population (12, 53), it is possible that these polymorphisms may have a physiological or pathophysiological role in beta-cell function. Thus an amino acid polymorphism on
codon 98 of the HNF-1α gene, observed in about 4% of Danish subjects regardless of the glucose tolerance status, was found to be associated with reduced insulin response to an oral glucose challenge in healthy young subjects (54).

Linkage of diabetes with the MODY1 region on chromosome 20q was also negative in a panel of 20 multigenerational white French families with NIDDM (55). Negative results were also observed with sib-pair analysis of a small panel of British and Italian sibs (56), but, here again, positive results were observed in the same set of 53 white American sibs-pairs who showed positive linkage with the MODY3 locus (51). Recently, we have identified one family with late age of onset NIDDM, in whom a mutation in HNF-4α/MODY1 co-segregated with deficient insulin secretion and diabetes (57). Thus it is clear from all these results that the role of MODY1 and MODY3 loci on late onset NIDDM is only beginning to be established.

Insulin promoter factor-1 and diabetes

The insulin promoter factor (IPF)-1, which is also known as IDX-1, STF-1 and PDX-1, is a homeodomain transcription factor that regulates pancreatic development and the expression of various beta-cell genes, including the insulin gene (58). It has been shown that the disruption of the IPF-1 gene in mice results in agenesis of the pancreas (59). Recently, a mutation in exon 1 of the IPF-1 gene (Pro63fsdelC), resulting in a truncated protein, was found to co-segregate with diabetes in a large kindred presenting a consanguineous link (60). The phenotype of those who are heterozygous for the mutation ranges from normal to impaired glucose tolerance, to overt non-insulin-dependent diabetes. The average age of onset of chronic hyperglycaemia in this kindred (35 years) is greater than in typical MODY kindreds, but it ranges from 17 to 67 years. One child who is homozygous for the mutation was born with pancreatic agenesis, and suffers from diabetes in addition to exocrine insufficiency (61). The role of IPF-1 in MODY and late-onset NIDDM remains to be investigated.

Conclusions

MODY is a genetically heterogeneous subtype of NIDDM characterised by early onset, autosomal dominant inheritance and a primary defect in insulin secretion. It seems to be a relatively frequent disorder, as recent studies suggest that 2–5% of patients with NIDDM may in fact have MODY. The role of the known MODY genes in the susceptibility to the more common late-onset NIDDM remain uncertain. Genetic studies seem to exclude a role as major susceptibility genes, but leave unresolved whether they may have a minor role in a polygenic context or an important role in particular populations. The nature or position of different mutations in these genes could explain diverse phenotypic presentations of diabetes. Mutations in sites affecting the function of the gene product in a major way might be sufficient to induce glucose intolerance early in life, regardless of the absence of other predisposing factors. Alternatively, mutations affecting this function only mildly could segregate in kindreds, without leading to hyperglycaemia at an early age. Later in life, other genetic or environmental factors could contribute to the development of diabetes. It is clear that further investigations in larger and well-phenotyped cohorts from different populations, stratified for particular phenotypes, are required to evaluate the role of the MODY genes in the common forms of NIDDM.

The identification of GCK as a diabetes susceptibility gene has provided a major impulse for the reassessment of the physiological role and the understanding of the pathophysiological importance of this key enzyme of glucose homeostasis. The recent identification of MODY1 and MODY3 as the genes encoding two physiologically related transcription factors opens entirely new perspectives in the understanding of the molecular basis, not only of MODY, but possibly also of other forms of NIDDM. It will contribute to our knowledge of glucose homeostasis and, possibly, to the definition of targets for new drugs for the treatment of diabetes. In this regard, MODY can be considered as a paradigm of NIDDM.

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