Maturity-onset diabetes of the young is a heterogeneous group of autosomal dominantly inherited, young-onset β-cell disorders. At least two consecutive generations are affected with a family member diagnosed before 25 years of age. Diabetes is caused either by mutations in the glucokinase gene (glucokinase MODY) or by mutations in transcription factors (transcription factor MODY). Glucokinase maturity-onset diabetes of the young is a mild, non-progressive hyperglycaemia caused by a resetting of the pancreatic glucose sensor. It is treated with diet, and complications are rare. Pregnancies affected by glucokinase mutations have specific management strategies and prognosis. Transcription factor maturity-onset diabetes of the young, caused by mutations in the hepatocyte nuclear factor genes HNF-1α, HNF-4α and HNF-1β, and in insulin promoter factor-1 results in a progressive β-cell defect with increasing treatment requirements and diabetic complications. Cystic renal disease is a prominent feature of HNF-1β mutations. Further maturity-onset diabetes of the young genes remain to be identified. MODY is part of the differential diagnosis of diabetes presenting in the first to third decades of life. Diagnostic molecular genetic testing is available for the more common genes involved.

**Key words:** MODY; glucokinase; HNF-1α; HNF-4α; HNF-1β; IPF-1; diagnostic testing.

Maturity-onset diabetes of the young (MODY) originally described familial, young-onset, non-insulin-dependent diabetes. We now use the term to describe monogenic forms of diabetes of beta cell origin, probably accounting for about 2% of non-insulin-dependent diabetes in Europe. This encompasses a diverse group, and considerable progress has been made over the past 10 years in defining the phenotypes of the different genes involved.

**Recognition of maturity-onset diabetes of the young and its clinical features**

It was historically observed that some children and young adults developed familial non-insulin-dependent diabetes and thus had prolonged survival in the pre-insulin era.
This was recognized as an autosomal dominant condition in 1974, when the original clinical features were described by Robert Tattersall:\(^1\):

1. **Early onset, non-insulin dependent diabetes.** At least one and ideally two family members are diagnosed before the age of 25 years. Those treated with insulin should have evidence of circulating C-peptide, indicating endogenous insulin secretion.
2. **Autosomal dominant inheritance.** There should be at least two generations with diabetes and ideally three generations and cousins showing a similar phenotype. Caution should be exercised if both parents have type 2 diabetes as the early-onset disease might then be the result of a ‘double gene dose’.\(^2\)

We now know that MODY is a heterogenous group of single-gene disorders. Mutations in five genes have been shown to cause MODY: the glycolytic enzyme glucokinase and the transcription factors hepatocyte nuclear factors (HNF)\(_{1\alpha}, -4\alpha\) and \(-1\beta\), and insulin promoter factor (IPF)\(_1\). The clinical and molecular characteristics of the syndromes caused by mutations in each gene are described in Table 1. Recent classifications of diabetes by the American Diabetes Association and the World Health Organization\(^3\) have recognized MODY as comprising discrete subtypes of diabetes arising from mutations in specific genes. MODY is therefore probably the first area in diabetes in which molecular genetics has had a clear clinical as well as a research role.

### Discovery of genes causing maturity-onset diabetes of the young

In contrast to those of type 2 diabetes, MODY genes were relatively simple to identify because the young age of onset meant that it was easy to collect multigenerational families for study. Another important difference is that, within each MODY family, only one gene causes diabetes with minimal environmental influence, whereas type 2 diabetes subjects may possess several genes that lead to an increased predisposition to developing glucose intolerance.

The identification of aetiological genes in MODY would not have been possible without the development of modern genetic techniques centred on the use of the polymerase chain reaction. The breakthroughs in defining the genetic aetiology came through the use of linkage methods. The glucokinase (MODY2) gene was defined in French and English MODY pedigrees in 1992 using a candidate gene approach.\(^4,5\)

The major breakthrough was, however, the use of positional mapping methodology, which identified loci on chromosome 20q (MODY1) and 12q (MODY3).\(^6,7\) The MODY3 gene on 12q was defined as HNF-1\(_\alpha\) by Bell’s group in Chicago.\(^8\) This was a significant finding because the HNF group of transcription factors had not previously been considered as candidate genes. The rapid recognition of HNF-4\(_\alpha\) as the MODY1 gene\(^9\) followed. Since HNF-1\(_\alpha\) forms heterodimers with HNF-1\(_\beta\), this gene was also highlighted as an excellent candidate gene, and mutations in the HNF-1\(_\beta\) gene (MODY5) were subsequently described.\(^10\) The description of IPF-1 as the MODY4 gene arose from observations in a family initially investigated because the proband had pancreatic agenesis, a condition seen in the IPF-1 knockout mouse.\(^11,12\)

The pathophysiology and phenotype of MODY caused by mutations in the glucokinase gene (glucokinase MODY) are quite different from those caused by either the transcription factor mutations (transcription factor MODY) or type 2 diabetes, leading to different management strategies. There are also a significant minority (10–15% but significantly more in Japan) of MODY families in whom mutations have not been found in any of the known genes. Although some of these families will have young-onset type 2 diabetes with multiple predisposing genes, it seems probable that
<table>
<thead>
<tr>
<th></th>
<th>Glucokinase (MODY 2)</th>
<th>HNF-1α (MODY 3)</th>
<th>HNF-4α (MODY 1)</th>
<th>HNF-1β (MODY 5)</th>
<th>IPF-1 (MODY 4)</th>
<th>MODY X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal location</td>
<td>7p</td>
<td>12q</td>
<td>20q</td>
<td>17q</td>
<td>13q</td>
<td>Unknown</td>
</tr>
<tr>
<td>Frequency in a large UK</td>
<td>15% 1%</td>
<td>13%</td>
<td>1%</td>
<td>5%</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>Penetration of mutations</td>
<td>45% diabetes 95%</td>
<td>&gt;90%</td>
<td>&gt;80%</td>
<td>? &gt;90%</td>
<td>Limited data</td>
<td>Unknown</td>
</tr>
<tr>
<td>at age 40 years</td>
<td>improved fasting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvascular</td>
<td>Early childhood</td>
<td>Adolescence</td>
<td>Similar to HNF-1α</td>
<td>Similar to HNF-1α</td>
<td>Early adulthood</td>
<td>Uncertain</td>
</tr>
<tr>
<td>complications</td>
<td>Early adulthood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Beta cell dysfunction</td>
<td>Beta cell dysfunction</td>
<td>Beta cell dysfunction</td>
<td>Beta cell dysfunction</td>
<td>Beta cell dysfunction</td>
<td>Beta cell dysfunction</td>
</tr>
<tr>
<td>Abnormality of glucose</td>
<td>Reduced birth weight</td>
<td>Low renal threshold and sensitivity to sulphonylureas</td>
<td>Low plasma triglyceride levels</td>
<td>Predominant renal phenotype: cysts, renal failure</td>
<td>Genital malformations</td>
<td></td>
</tr>
<tr>
<td>sensing</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>
there are one or more MODY genes left to identify, possibly in novel pathways (see below).

**Differential diagnosis in children and young adults**

Until recently, the subclassification of diabetes into types 1 and 2 was mainly made on the basis of age at diagnosis. With an increasing awareness of MODY as a discrete diagnosis and a significant rise in prevalence of type 2 diabetes presenting in the second and third decade, however, clinicians must consider alternatives to type 1 diabetes. Some of the important distinguishing properties of the different aetiologies are shown in Table 2. The composition of the local population will affect the prevalence of each of these; in under-25-year-olds, for example, MODY is much more common than type 2 diabetes in the UK Caucasian population, but the situation will be reversed in populations with a high prevalence of type 2 diabetes. As the current clinical understanding of MODY implies a beta cell defect, peripheral insulin resistance and obesity are not usually features of MODY. Therefore the presence of acanthosis nigricans or features of the metabolic syndrome should prompt consideration of a different aetiology.

Some patients with MODY are misdiagnosed as having type 1 diabetes because they present in their second or third decade with osmotic symptoms. The main differentiating features are:

1. an autosomal dominant family history;
2. the absence of typical type 1 human leukocyte antigen markers and beta cell antibodies;
3. excellent glycaemic control despite relatively low doses of insulin (usually less than 0.5 units/kg);
4. no report of ketoacidosis, even when insulin is omitted (although, like type 2 diabetes, this could potentially happen in severe circumstances).

Making the correct diagnosis relies on a combination of clinical features, a knowledge of the family history and laboratory testing.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1</th>
<th>Type 2</th>
<th>MODY</th>
<th>Mitochondrial Diabetes (MIDD)</th>
<th>Genetic obesity syndromes (eg Prader – Willi)</th>
<th>Severe insulin resistance syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected parent</td>
<td>0–1</td>
<td>1–2</td>
<td>1</td>
<td>Mother</td>
<td>Not usual</td>
<td>Depending on inheritance</td>
</tr>
<tr>
<td>Obesity</td>
<td>Not usual</td>
<td>Usual</td>
<td>Not usual</td>
<td>Not usual</td>
<td>Present</td>
<td>Not usual</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>No</td>
<td>Frequent</td>
<td>No</td>
<td>No</td>
<td>May be present</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Antibodies to pancreatic beta cells</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Genetic testing appropriate</td>
<td>Not usually</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

MODY = maturity-onset diabetes of the young; MIDD = maternally inherited diabetes and deafness.

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**Table 2. Classification of diabetes presenting in the first to third decades of life.**
GLUCOKINASE (MODY2)

Glucokinase was an obvious candidate gene for diabetes because of its central role in carbohydrate metabolism. As one of the hexokinase family, it catalyses the first reaction of the glycolytic pathway, the conversion of glucose to glucose-6-phosphate. Glucokinase is principally expressed in pancreatic beta cells and in hepatocytes. In beta cells, this step is closely linked to the initiation of insulin secretion. The kinetics of the enzyme, with a $K_m$ of 5 mmol/l plasma glucose concentration, allow beta cells to change the glucose phosphorylation rate over a range of physiological glucose concentrations (4–15 mmol/l), thus acting as the pancreatic glucose sensor. The e/C128ect of glucokinase mutations on insulin secretion is expressed diagrammatically in Figure 1a. The curve is of a similar shape but parallel to the normal curve, so a given insulin response requires a higher ambient glucose concentration. This concept explains many of the observations seen in glucokinase MODY.

There are over 100 published mutations of glucokinase distributed throughout the 12 exons of the gene, none being particularly more frequent than any other. They cause decreased affinity of the enzyme for glucose and lead to hyperglycaemia with an identical phenotype. One mutation causes the opposite phenotype – hypoglycaemia secondary to hyperinsulinaemia because of an increased affinity for glucose.

The glucokinase phenotype

Subjects with glucokinase mutations have lifelong, mild fasting hyperglycaemia that does not significantly progress with age. The majority of patients have blood glucose values within a narrow range of 6–8 mmol/l, values above 10 mmol/l being unusual. It is highly
uncommon for the fasting glucose level to be less than 5.5 mmol/l; if this is so on repeated testing, glucokinase mutation is virtually excluded. A characteristic feature of glucokinase diabetes is a small increment between the fasting and 2 hour values on an oral glucose tolerance test, with a mean value of 2.4 mmol/l.\textsuperscript{16} This provides a useful discriminator from transcription factor MODY, in which the mean increment is 8.5 mmol/l.\textsuperscript{16}

Because of the mild nature of the hyperglycaemia, patients are rarely symptomatic, most being diagnosed during routine screening. They may not meet the diagnostic criteria for diabetes, or they may be classified as gestational diabetes, impaired glucose tolerance, MODY or type 2 diabetes according to the circumstances that led to testing. In glucokinase, more than in any other type of diabetes, the age of diagnosis may be decades after the age of onset, so many glucokinase families do not meet classical MODY criteria with a diagnosis under the age of 25.

Patients with glucokinase mutations have been shown to have a beta cell dysfunction caused by a defect in glucose sensing.\textsuperscript{17,18} The first-phase insulin response to an intravenous or oral glucose bolus is well preserved.\textsuperscript{19,20} Patients with glucokinase mutations have reduced hepatic glycogen synthesis, showing that glucokinase is also a rate-determining step in the liver.\textsuperscript{21}

The mild hyperglycaemia and small increase in blood glucose level in response to oral carbohydrate means that dietary vigilance to avoid excessive post-prandial hyperglycaemia is the only treatment required for glucokinase MODY. More than 85% of patients are managed on diet alone, and some diagnosed in childhood have been able to stop insulin treatment begun on the assumption that they had type 1 diabetes. In contrast to patients with type 2 diabetes or HNF-1\textsubscript{a} mutations, body weight makes little difference to the level of glycaemia in patients with glucokinase mutations.\textsuperscript{17} This is because hyperglycaemia is caused by a defect in glucose sensing rather than a failure of insulin secretion; therefore, as in the normal subject, increased insulin resistance as a result of obesity results in compensatory hyperinsulinaemia rather than hyperglycaemia.

Microvascular complications are extremely unusual in patients with glucokinase mutations\textsuperscript{17,22} because of the mild hyperglycaemia. Rarely, diabetic retinopathy has been reported in French patients, but this may represent coincidental type 2 diabetes in patients who also have a glucokinase mutation.

Features of the metabolic syndrome are not generally seen, insulin concentration and plasma lipid levels being normal.\textsuperscript{17} Macrovascular complications have not been widely reported, although patients may, in common with other subjects with impaired glucose tolerance, be at increased risk. However, their lack of insulin resistance, normal lipid levels and narrow glycaemic excursions are likely to reduce the risk still further.

One area of uncertainty is the degree of medical supervision necessary for patients with glucokinase MODY. A close follow-up of children who have only a mildly elevated fasting glucose level is certainly not warranted, and repeated contact with a diabetic clinic predominantly dealing with type 1 diabetes may be detrimental. We cannot assume that older patients will not have diabetic complications, particularly as these patients could develop polygenic type 2 diabetes. An annual follow-up of adults by measuring their glycated haemoglobin (HbA\textsubscript{1c}) level is probably all that is required. Only the few patients with an elevated HbA\textsubscript{1c} will require more careful follow-up.

**Glucokinase mutations and pregnancy**

Study of babies born to parents with glucokinase mutations has presented us with a fascinating insight into the interaction of the maternal and fetal genetics involved in
intra-uterine growth. Glucokinase mutations are found in up to 6% of diabetic pregnancies. This is frequently the first presentation of the mutation, detected on routine screening. The recognition of glucokinase mutation subjects is important because they have a different clinical course both within and outside pregnancy compared with most other subjects with gestational diabetes. In addition, there is a 50% risk that the offspring will be affected.

Insulin is an important determinant of fetal growth in all pregnancies, particularly during the third trimester. The maternal glucose level stimulates fetal insulin secretion, and diabetic pregnancies thus lead to macrosomia. In a glucokinase pregnancy, however, the effect of the maternal glucose level will depend on whether or not the fetus has inherited the mutation. Figure 1b above shows the effect of the fetal genotype on fetal insulin secretion. If the fetus has a normal genotype, the result will be similar to that of a normal diabetic pregnancy resulting in a large baby. If, however, the mutation has been inherited, the mother’s blood glucose level will be at a level appropriate to stimulate fetal glucokinase, thus producing a normal pattern of growth. In this case, treatment of the mother with insulin to lower her blood glucose level to normal will have a detrimental effect on fetal growth, resulting in a small baby. The latter effect is also seen when a fetus inherits a glucokinase mutation from the father.

Patients’ clinical characteristics can be used to detect those with a history of gestational diabetes who are most likely to have a glucokinase mutation. The specific criteria favouring a diagnosis of a glucokinase mutation are:

1. persistent fasting hyperglycaemia;
2. a small (less than 3 mmol/l) increment on the oral glucose tolerance test;
3. a family history of mild hyperglycaemia.

When these features were used to select patients for glucokinase mutation screening, 80% of those tested were found to have a mutation.

Glucokinase and neonatal diabetes

Two cases have been reported of homozygous glucokinase mutations causing permanent neonatal diabetes that requires insulin treatment from birth. This should not be confused with the mild fasting hyperglycaemia detectable from birth in heterozygotes.

Transcription Factor MODY

The role of hepatocyte nuclear factor (HNFs) in the pancreas had not been studied prior to their discovery as MODY genes. The mechanism by which they cause diabetes is still unknown but probably involves beta cell development pathways as well as disrupting the expression of important beta cell genes. Mutations in the genes of transcription factors HNF-1α and-4α cause diabetes with a similar phenotype. Mutations of both HNF-1β and IPF-1 are extremely rare causes of MODY, so defining the phenotype of the diabetes associated with them is less clear than with the other genes. The clinical features caused by alterations of HNF-1β are dominated by renal abnormalities.

HNF-1α (MODY3)

Mutations in the HNF-1α gene are the most common cause of MODY, confirmed by the detection of mutations in European, North American and Japanese populations.
There are over 100 different mutations scattered throughout the gene, comprising frameshift, missense, nonsense and splice-site mutations. Approximately 15% of HNF-1α families have the same mutation – a C-insertion (P291fsinsC) in exon 4. This is thought to be a hotspot for mutations rather than a founder effect.

**Phenotype of HNF-1α mutations**

In contrast to those with glucokinase MODY, patients with HNF-1α mutations have a normal fasting glucose level in childhood but develop progressive hyperglycaemia in adolescence and early adulthood. They usually present with symptomatic diabetes, have increasing treatment requirements and frequently develop microvascular complications. As the primary pathophysiology is a beta cell defect, features of the metabolic syndrome are unusual in this group.

HNF-1α mutations have a high penetrance, the majority of subjects having diabetes by 25 years of age. Figure 2 shows the prevalence of diabetes with age. Some subjects with HNF-1α mutations are not diagnosed until middle or old age, which may be because of either a delayed diagnosis or a later onset of diabetes. The mutation carriers who are non-diabetic on testing are usually young and are likely to develop diabetes later in life. There are some individuals who have reached early middle age without having diabetes, these unusual cases probably representing true non-penetrance of the gene. These subjects frequently have a low body mass index and so can compensate for their beta cell defect by being sensitive to the insulin they do produce.

HNF-1α patients show a progressive beta cell defect. In those not yet diabetic, studies have shown they have an adequate insulin level when fasting but are unable to increase their insulin secretion as the glucose level rises. Prolonged (18 hours) hyperglycaemia primes the beta cell in these non-diabetic individuals. Once patients

Figure 2. Percentage of mutation carriers with diabetes against age, showing the penetrance of the HNF-1α mutation. Reproduced from Shepherd et al (2001 Practical Diabetes 18: 16–21) with permission.
have established diabetes, insulin secretion is reduced. Unlike the situation with glucokinase, there is no defect in the sensing of glucose.

As HNF-1α patients develop severe diabetic complications, they require regular medical follow-up comparable to that employed with type 1 diabetes.

**Special Features of HNF-1α MODY**

**Sensitivity to sulphonylureas.** Patients with HNF-1α mutations can show a marked sensitivity to the hypoglycaemic action of sulphonylureas. This is particularly noticeable at diagnosis and may result in symptomatic hypoglycaemia when starting therapy. Although metformin and the sulphonylureas are equally effective in reducing HbA₁c in most subjects with type 2 diabetes, this appears not to be the case in patients with HNF-1α mutations. Case reports have noted a marked deterioration in glycaemic control on transferring from sulphonylureas to metformin, with an improvement in HbA₁c level of 4–5% on returning to sulphonylureas. Therefore, low-dose sulphonylureas are the appropriate first-line medication for patients with HNF-1α mutations. This is probably the first example of pharmacogenetics in diabetes and is a clear reason for establishing the aetiology of young-onset, non-insulin-dependent diabetes.

**Low renal threshold for glucose.** In the early descriptions of MODY, it was noticed that there was a discrete subgroup of MODY families who had a low renal threshold that was apparent prior to the development of diabetes. It has now been shown that these patients had a mutation in HNF-1α and that a low renal threshold is a feature of other patients with HNF-1α mutations. Experiments in the HNF-1α knockout mouse suggest this is probably the result of a reduced expression of the high-capacity/low-affinity sodium–glucose transporter-2, reducing glucose re-absorption in the proximal tubule.

**HNF-4α (MODY1)**

Before the discovery of the other MODY genes, it was known that the MODY1 gene localized to chromosome 20q. This was possible because of extensive study by Fajans and colleagues of the large RW pedigree, who have MODY caused by a mutation in this gene. After HNF-1α had been identified as the MODY3 gene, the closely related transcription factor HNF-4α was shown to be within the area identified by linkage.

Mutations in the HNF-4α gene are a rare cause of diabetes compared with those in glucokinase and HNF-1α with only 12 mutations having been reported world wide. The phenotype of HNF-4α MODY is very similar to that of HNF-1α, although the penetrance may be slightly lower. It is not possible to distinguish the diabetes caused by the two genes on clinical criteria. There is a progressive beta cell failure with increasing treatment requirements and the development of microvascular complications.

In contrast to the situation with HNF-1α, sulphonylurea sensitivity and a low renal threshold have not been reported in these patients. The main extra-pancreatic manifestations described result from a reduced transcription of the hepatic target genes of HNF-4α. A reduced concentration of the apolipoproteins apoAll, apoCIII and possibly apoB are found in patients with HNF-4α MODY. Triglyceride levels are reduced compared with type 2 diabetes; this probably reflects reduced lipoprotein lipase activity as a result of the reduced apolipoproteins.
HNF-1β (MODY5)

Although a good candidate gene, it soon became clear through the screening of MODY pedigrees that HNF-1β mutations were not a common cause of MODY. The first HNF-1β mutations were found in families who were noted to have non-diabetic renal dysfunction. Screening families with renal disease and early-onset diabetes has revealed several new mutations and their associated renal phenotypes. Patients with HNF-1β mutations more frequently present in the renal clinic than in the diabetes clinic.

Renal manifestations of HNF-1β mutations

Non-diabetic cystic renal disease is a feature of all HNF-1β mutations where renal tract imaging has been performed. This has led to the description of a new syndrome caused by HNF-1β mutations: Renal Cysts and Diabetes (RCAD). Three discrete histologies have been described: oligomeganephronia, cystic dysplasia and familial hypoplastic glomerulocystic kidney disease. The renal manifestations are the result of abnormal nephron development, and the aberrant renal morphology may be observed on scans as early as 17 weeks of pregnancy. It is uncertain what determines the morphology of the renal defect, but it probably reflects the functional characteristics of the mutation.

Within families, the severity of the renal disease can be quite variable, ranging from asymptomatic cysts to renal anomalies incompatible with survival. Approximately 50% of subjects will develop end-stage renal failure before the age of 45. In many subjects, the renal manifestations are first detected in young children, presenting decades before the development of diabetes. This probably explains why it was not appreciated that diabetes was a feature of familial hypoplastic glomerulocystic kidney disease. Other developmental disorders including genital abnormalities, prognathism and pyloric stenosis, have been seen in association with HNF-1β mutations.

HNF-1β diabetes

HNF-1β mutations result in early-onset, non-insulin-dependent diabetes with a severity similar to that seen in patients with mutations of HNF-1α. Children and young adults have been described with normal or impaired glucose tolerance, suggesting that there is a progressive deterioration in beta cell function. The mean age of diagnosis is in the early 20s. Physiological studies in a single subject showed a beta cell defect, and it is likely that this is the pathophysiology in all subjects. Subjects have been described with proliferative retinopathy.

IPF-1 (MODY4)

IPF-1 is a good candidate gene for diabetes because it has a pivotal role in pancreatic development and the maintenance of the beta cell phenotype. In IPF-1 knockout mice, the pancreas is absent, and the disruption of IPF-1 after the development of the beta cells leads to diabetes. It has, however, been found to cause MODY in only one extended family, who had a child with pancreatic agenesis caused by a homozygous IPF-1 mutation. In both sides of the family (who may have been related), the possession of one copy of the mutation co-segregated with diabetes, with an average age of onset of 35 years. The family fitted MODY criteria, one individual having been diagnosed at 17 years.
The search for IPF-1 mutations in other MODY pedigrees from France\textsuperscript{46}, the UK\textsuperscript{47} and Japan\textsuperscript{48} has been negative, suggesting that mutations that cause MODY are rare. There is, however, evidence that milder missense mutations in IPF-1 predispose to type 2 diabetes\textsuperscript{47,49,50}, particularly that of young-onset. In one French family, there was co-segregation with diabetes, and apparently unaffected individuals with the IPF-1 mutations showed either diabetes or impaired glucose tolerance on the basis of 2 hour glucose values. Insulin secretion, particularly first-phase insulin secretion, was markedly reduced\textsuperscript{49}.

These data suggest that mutations in IPF-1 result in reduced beta cell function. The effect is in general much less severe than that seen with HNF-1\(\alpha\) mutations, and young adults who are insulin sensitive may not be diabetic despite having a reduced insulin secretion in response to a glucose load. It is probable that a variation of the severity of the mutation explains, at least to some extent, the variation in phenotype. IPF-1 mutations may well more frequently be part of a polygenic predisposition to young-onset type 2 diabetes rather than the simple monogenic aetiology seen in MODY.

**MODY X**

Mody X families fit MODY criteria but do not show a linkage to any of the known MODY genes. A heterogeneity between families in this group suggests that more than one additional gene may remain undiscovered\textsuperscript{51}. In the absence of an underlying genetic defect, it is difficult to make precise statements on the phenotype. Some families who do not have a mutation in the known MODY genes have been defined by less rigorous criteria. In such families, diabetes may result from a high concentration of polygenic influences rather than a single gene.

Some pedigrees show a linkage to MODY genes but do not have variations in the coding regions. Regulatory regions may contain mutations: a mutation in the HNF-4\(\alpha\) binding site of the HNF-1\(\alpha\) promoter, for example, co-segregated with diabetes in an Italian MODY family\textsuperscript{52}. As four out of the five known MODY genes are transcription factors, these are important candidate genes for MODY X. In particular NeuroD1, Nkx2.2 and HNF-3\(\beta\) have been targets for investigation because of their role in pancreatic gene expression supported by work in transgenic animals. A NeuroD1 missense mutation has been shown to co-segregate with diabetes in a family who fitted MODY criteria\textsuperscript{53}, but screening for mutations causing MODY in these transcription factors has otherwise been negative.

Future research will focus on linkage studies in large MODY X pedigrees and the investigation of candidate genes within the loci identified. The key candidate genes for MODY are likely to be those involved in gene transcription, pancreatic development or glucose sensing in the pancreatic islet.

**DIAGNOSTIC TESTING IN MODY**

Diagnostic molecular genetic testing is now available in the UK and other European countries. The clinical management of patients is assisted by knowledge of the molecular genetic diagnosis; for example, a 12 year old with a slightly raised fasting glucose has a very different clinical course and treatment depending on whether they have a glucokinase mutation, a mutation in HNF-1\(\alpha\) or type 1 diabetes. A diagnosis of MODY predicts treatment choice, likely prognosis and allows genetic counselling for family members.
Genetic testing can also predict whether first-degree relatives are likely to develop MODY in the future, particularly valuable in an unaffected young adult. Testing of young children may also be beneficial but this is considerably more controversial. Full genetic counselling should be provided for individuals who seek predictive testing.

Diagnostic testing is usually requested on the basis of clinical features (Table 2), and is commonly available for the two genes that most frequently cause MODY, \( HNF-1\alpha \) and glucokinase. Currently, because mutations are spread throughout the genes, sequencing of the entire gene is required, which is time consuming and expensive. This situation is likely to improve as technology advances. We believe that for many patients, the expense is justified by enhanced clinical management.

The individuals most likely to have MODY are from families where a child or young adult with diabetes is not dependent on insulin and they have a parent with diabetes or hyperglycaemia. Testing of families fitting traditional MODY criteria, with diagnosis under the age of 25 and 2 or 3 generations of diabetes, leads to a high yield of positive tests – in the region of 50% for \( HNF-1\alpha \) testing in our diagnostic service. Diabetes due to Glucokinase mutations may be considered for individuals presenting at any age who have the characteristic phenotype outlined on pages 313–314.

Evidence of beta cell autoimmunity makes type 1 diabetes very likely and, in these circumstances, genetic testing is unlikely to be helpful.

**SUMMARY**

MODY is a heterogenous group of autosomal dominantly inherited, young-onset beta cell disorders that account for approximately 2% of non-insulin-dependent diabetics in Europe. Classically, there should be at least two consecutive generations of diabetes with a family member diagnosed before 25 years of age. MODY can be divided into two major subgroups (glucokinase and transcription factor MODY), which have differing features and management strategies.

Glucokinase MODY is a mild non-progressive hyperglycaemia caused by a resetting of the pancreatic glucose sensor. Fasting hyperglycaemia is the norm with a small increment on oral glucose tolerance testing. This kind of diabetes is characteristically treated with diet, and complications are rare. Pregnancy in women with glucokinase MODY represents an unusual type of gestational diabetes in which the fetal genotype has an important contribution to the outcome.

Transcription factor MODY caused by \( HNF-1\alpha \), \( -4\alpha \), \( -1\beta \) and \( IPF-1 \) mutations results in a progressive beta cell defect leading to increasing treatment requirements and the development of diabetic complications. \( HNF-1\alpha \) mutations are the most common cause of MODY in most populations. \( HNF-1\beta \) mutations cause predominantly non-diabetic cystic renal disease with diabetes as a secondary feature, known as Renal Cysts and Diabetes. The epithet ‘autosomal dominant renal cysts and diabetes’ describes this syndrome. \( IPF-1 \) mutations are a rare cause of MODY but may contribute to an increased risk of type 2 diabetes.

Evidence suggests that at least one further gene causes MODY and candidate genes include other beta cell transcription factors. Future studies will focus on linkage studies in MODY X families to identify new loci for MODY genes.

MODY should be considered in the differential diagnosis of diabetes presenting in the first to third decades of life. Establishing a diagnosis of MODY has implications for management. Diagnostic molecular genetic testing is available for the more common MODY genes.
Practice points

- MODY is part of the differential diagnosis of diabetes presenting in the first to third decades of life
- the two major subgroups of MODY are caused by glucokinase gene mutations and transcription factor gene mutations
- MODY causes a beta cell defect, so features of the metabolic syndrome are not usually observed
- a family phenotype of mild diabetes, gestational diabetes and a small increment on oral glucose tolerance testing suggests glucokinase MODY
- a family phenotype of progressive diabetes with microvascular complications and a large increment on oral glucose tolerance testing suggest transcription factor MODY
- a family or personal history of cystic renal disease and diabetes suggests an HNF-1β mutation

Research agenda

Current research in MODY focuses on the following areas:

- a further study of the phenotypes of MODY subgroups to aid clinical diagnosis and management
- developing more efficient methods to detect mutations in the known MODY genes
- understanding the mechanisms that result in MODY mutations causing beta cell dysfunction
- investigating the role of variations in the regulatory regions of known MODY genes in both MODY and type 2 diabetes
- defining new genes that cause MODY using both a reverse genetic and a candidate gene approach. Other beta cell transcription factor genes are excellent candidate genes
- devising successful strategies for integrating molecular genetic testing for MODY with clinical care
- examining the social and psychological effects of diagnostic and predictive genetic testing in MODY

REFERENCES


