4 Other Types of Diabetes

15 Monogenic Causes of Diabetes

Angus Jones & Andrew T. Hattersley
Diabetes and Vascular Medicine, Peninsula Medical School, Exeter, Devon, UK

Keypoints

- Monogenic diabetes results from single-gene mutations that cause β-cell dysfunction or, less commonly, insulin resistance.
- Approximately 1–2% of diabetes is monogenic, but this is frequently misdiagnosed.
- Monogenic diabetes should be suspected where: presentation is atypical for type 1 or 2 diabetes; there is an autosomal dominant (or maternally inherited in mitochondrial disorders) family history; there are characteristic associated features such as deafness in mitochondrial diabetes or fat loss in lipodystrophy; or diabetes has been diagnosed within the first 6 months of life.
- Mutations in the glucokinase gene, which is important in "sensing" blood glucose levels in the pancreas, result in resetting of fasting glucose to a higher level (5.5–8.0 mmol/L). Patients have dominantly inherited mild fasting hyperglycemia with only modest changes in glycated hemoglobin. Complications are rare and no treatment is needed.
- Mutations in the transcription factor genes *HNF1A* and *HNF4A* result in dominantly inherited progressive hyperglycemia with symptomatic diabetes in adolescence or young adulthood. Patients with *HNF1A* or *HNF4A* diabetes are very sensitive to sulfonylurea treatment and may not require insulin until middle or old age.
- Mitochondrial mutations can result in maternally inherited diabetes often with sensorineural hearing loss and a range of other disorders.
- Diabetes diagnosed before 6 months is unlikely to be type 1 diabetes and a genetic cause should be sought even where the patient is now an adult. High dose sulfonylurea treatment is often more effective than insulin where mutations affecting Kir6.2 and SUR1 subunits of the β-cell potassium channel are identified.
- Acanthosis nigricans is the key feature of insulin resistance and a genetic cause should be considered where this is seen in non-obese patients. Partial lipodystrophy results in thin muscular limbs with hypertriglyceridemia and insulin resistance and suggests a mutation in *LMNA* or *PPARG*. In the absence of lipodystrophy an insulin receptor mutation is the most common cause.

Introduction

Monogenic diabetes results from inheritance of one or more mutations in a single gene and accounts for 1–2% of diabetes cases. Mutations may be inherited in a dominant or recessive fashion. The majority (90%) of monogenic diabetes cases are initially misdiagnosed as type 1 (T1DM) or type 2 diabetes (T2DM).

Correct genetic diagnosis is important to predict clinical course, explain other associated clinical features, enable genetic counseling and diagnose family members, and most importantly guide appropriate treatment.

Monogenic diabetes where the primary disorder affects the β-cell has four main clinical presentations: familial mild fasting hyperglycemia (glucokinase maturity-onset diabetes of the young [MODY]), familial young-onset diabetes (transcription factor MODY), neonatal diabetes and diabetes with extrapancreatic features. Clinical and biochemical features that help differentiate the common forms of monogenic diabetes that result in β-cell dysfunction from T1DM and T2DM are summarized in Table 15.1. Clinical features and management of monogenic diabetes without extrapancreatic features are further summarized in Figure 15.1. Single-gene mutations may also cause diabetes through insulin resistance as occurs in the inherited lipodystrophies and insulin receptor mutations. A number of monogenic multisystem diseases (e.g. hemochromatosis and cystic fibrosis) may cause diabetes; these are beyond the scope of this chapter and are discussed elsewhere (see Chapter 18).

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Maturity-onset diabetes of the young

Maturity-onset diabetes of the young (MODY) is autosomal dominantly inherited diabetes that, despite a young age of onset, is not insulin dependent [1,2]. It results from β-cell dysfunction rather than insulin resistance [1]. The underlying genetic etiology has now been defined that allows MODY to be subclassified according to the gene involved [3,4]. Mutations in at least eight genes have been linked to MODY [5,6]. These include mutations

Table 15.1 Differentiating β-cell monogenic diabetes from type 1 and 2 diabetes.

Features	Type 1 diabetes	Young type 2	*GCK* MODY	*HNF1A* MODY	MIDD	K_{ATP} PNDM
Insulin dependent	Yes	No	No	No	+/–	Yes
Parent affected	2–4%	Usually	Yes	Yes	Mother	15%
Typical age of onset	6 months – young adult	Adolescent and young adult	Birth (may be diagnosed at any age)	Teens – young adult	Young adult	Under 6 months
Obesity	Pop freq	Yes	Pop freq	Pop freq	Rare	Pop freq
Acanthosis nigricans	No	Yes	No	No	No	No
Glycemia	High	Variable	Mild	High	Variable	High
β-Cell autoantibodies	Usually	Sometimes	No	No	No	No
Typical C peptide (pmol/L)	<200 Outside honeymoon period	500–>1000	100–900	100–700	<100–700	<200

DM, diabetes; GCK, glucokinase; *HNF1A*, hepatocyte nuclear factor 1A (*HNF4A* is similar); MIDD, maternally inherited diabetes and deafness; PNDM, permanent neonatal diabetes; Pop freq, population frequency (frequency of obesity seen in the general population).

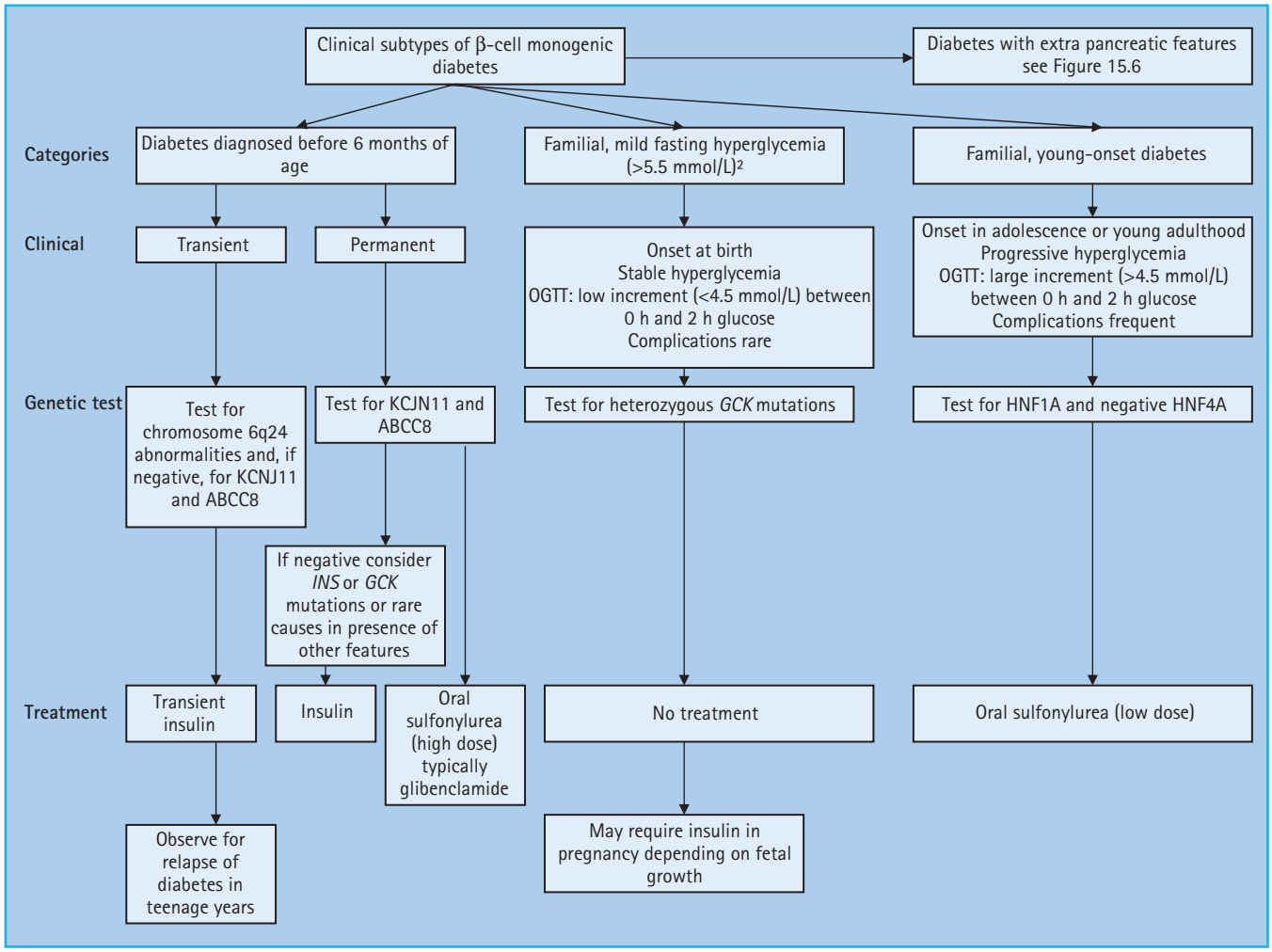

Figure 15.1 Clinical subtypes and management of monogenic β-cell diabetes without extrapancreatic features. To convert plasma glucose measurements to mg/dL multiple by 18. ABCC8, ATB binding cassette subfamily C; *GCK*, glucokinase gene; HNF, hepatocyte nuclear factor; *INS*, insulin gene; *KCNJ11*, potassium inwardly rectifying channel, subfamily J, member 11 gene; OGTT, oral glucose tolerance test.

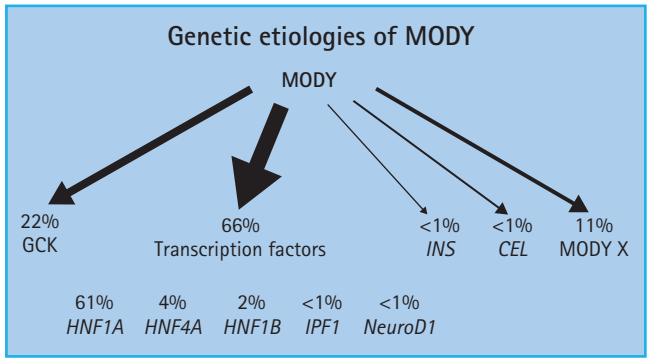

Figure 15.2 The different genetic etiology in a UK maturity-onset diabetes of the young (MODY) series. MODY X denotes dominantly inherited young-onset non-insulin dependent diabetes fitting clinical criteria for maturity-onset diabetes of the young where mutations in known MODY genes have not been identified. Adapted from McCarthy & Hattersley [6].

in the gene encoding the glucose sensing enzyme glucokinase (*GCK*) and mutations in several transcription factors that affect β-cell development and function, the frequencies of which are summarized in Figure 15.2. Clinical presentation varies greatly depending on the underlying genetic mutation. Table 15.2 summarizes the clinical features of glucokinase and transcription factor diabetes. The strikingly different subtypes of MODY mean it is important to define the underlying genetic etiology. We recommend the use of clinical categories based on underlying genetic cause – familial mild fasting hyperglycemia resulting from glucokinase gene mutations (*GCK* MODY), familial young-onset progressive diabetes resulting from *HNF1A* and *HNF4A* mutations (transcription factor MODY) and renal cysts and diabetes syndrome (RCAD) resulting from *HNF1B* mutations.

Mutations in the genes associated with MODY should be sought in patients with diabetes diagnosed under 25 years of age, who do not fully fit the phenotypes of T1DM or T2DM and who have a strong family history of diabetes (Table 15.1). Differentiating from apparent T1DM is particularly important as these patients can often be most effectively treated without the use of injected insulin.

Glucokinase MODY

Glucokinase catalyzes the phosphorylation of glucose to glucose-6-phosphate, the first and rate-limiting step in intracellular glucose metabolism in both β-cells and hepatocytes (Figure 15.3). Owing to the unique catalytic properties of the enzyme, the rate of glucose phosphorylation is proportional to the glucose concentration, thus allowing β-cells and hepatocytes to respond to changes in glycemia. In the β-cell, glucokinase acts as a glucose sensor ensuring insulin release is appropriate to the glucose concentration [7]. Heterozygous loss-of-function mutations in *GCK* result in a shift of the dose–response curve to the right [8].

Table 15.2 Comparison of the clinical characteristics of glucokinase and transcription factor maturity-onset diabetes of the young (MODY).

	Glucokinase MODY	Transcription factor MODY
Onset of hyperglycemia	Birth	Adolescence/early adulthood
Presentation	Usually asymptomatic, detected by screening or on routine testing	Usually symptomatic
Nature of hyperglycemia	Minimal increase in glycemia with age Mild (FPG usually 5.5–8 mmol/L) HbA_{1c} usually close or just above upper limit of normal	Progressive deterioration of glycemia with age May be severe (FPG frequently >14 mmol/L off treatment) HbA_{1c} variable depending on age and treatment, may be high
Pattern in an oral glucose tolerance test	FPG >5.5 mmol/L (2 hour – FPG) usually <3.5 mmol/L	FPG often <5.5 mmol/L (2 hour – FPG) usually >3.5 mmol/L
Microvascular complications	Rare	Frequent
Pathophysiology	β-Cell defect (glucose sensing defect)	β-Cell defect (initially insulin secretion maintained at normal glucose values but not increased in hyperglycemia)
Extrapancreatic manifestations	Reduced birth weight	See Table 15.3
Treatment	Pharmacologic treatment rarely needed	Sensitive to sulfonylurea treatment May progress to require insulin

FPG, fasting plasma glucose.

Glycemia is therefore regulated at a higher setpoint but remains tightly controlled. Subjects are still able to stimulate their β-cells maximally [8]. Glucokinase is also present in the liver and as a result patients have reduced hepatic glycogen synthesis [9].

Over 200 loss-of-function mutations in *GCK* have been identified, all causing a similar clinical picture. Homozygous loss-of-function glucokinase mutations are a rare cause of insulin-requiring diabetes presenting in the neonatal period [10]. Gain-of-function mutations cause congenital hyperinsulinism [11].

Clinical features

Patients have mild fasting hyperglycemia from birth, usually 5.5–8.0 mmol/L. There is only minor deterioration in fasting glucose with age (Figure 15.4) [12]. Patients do not have symptoms of hyperglycemia. Post meal glucose values are only mildly raised and there is frequently only a small increase (<3 mmol/L in 70% of patients) seen at 2 hours on an oral glucose tolerance test [13] which may explain the near normal HbA_{1c} and rarity of complications [14]. Glycated hemoglobin values above 7.5% would be suggestive of an alternative diagnosis. Marked worsen-

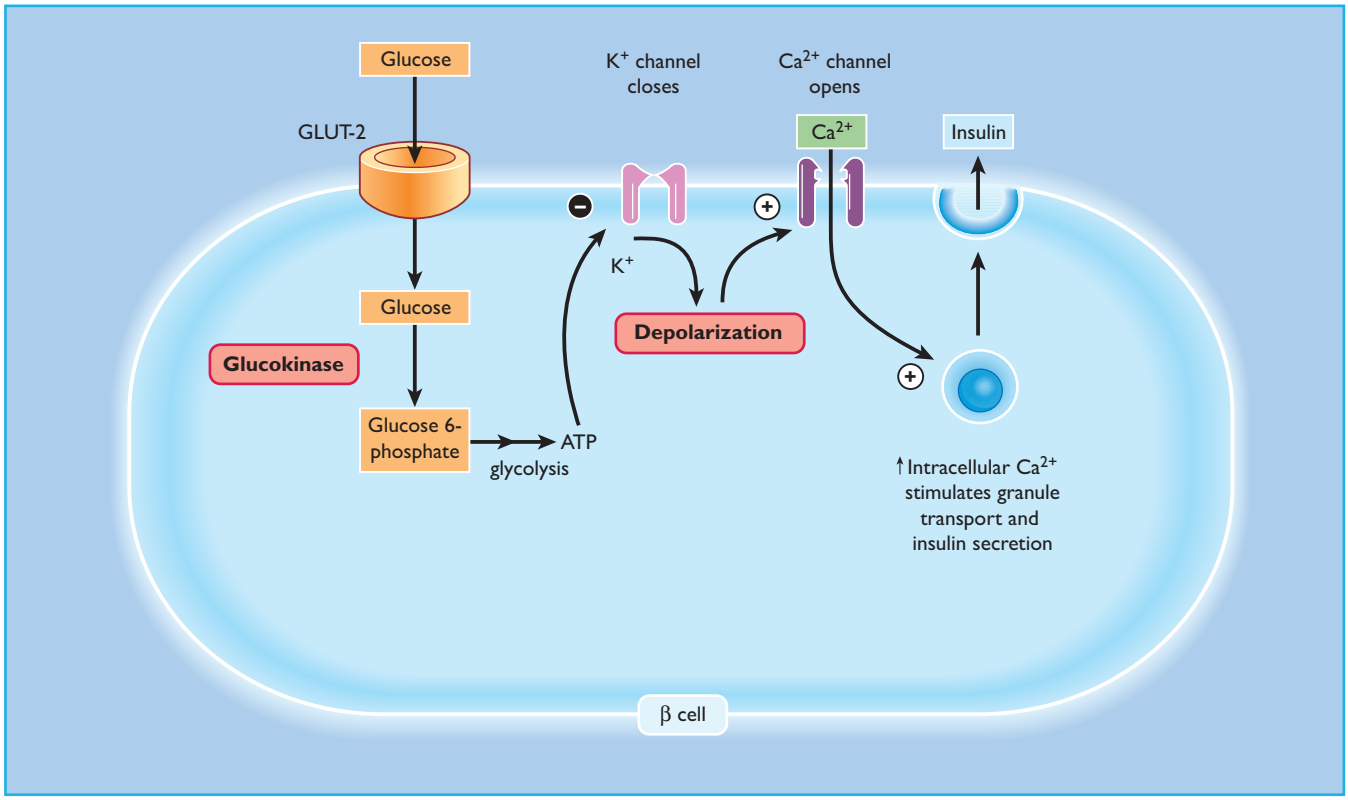

Figure 15.3 Glucokinase and its role within the β-cell. Glucokinase is the rate determining step in glucose metabolism, and therefore in the rate of production of ATP, which leads ultimately to insulin secretion.

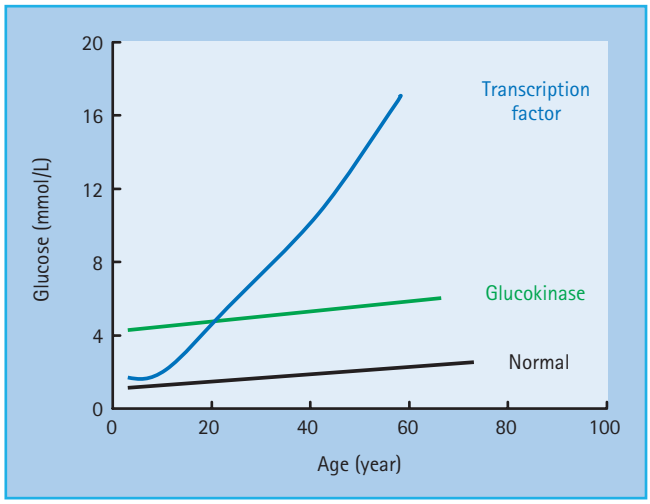

Figure 15.4 Variation of blood glucose concentration with age in patients with glucokinase and transcription factor MODY.

ing of the glycemia suggests that the patient has developed T1DM or T2DM in additon to their *GCK* mutation. Microvascular and macrovascular complications are rare even when no treatment is given [14]. Glucokinase MODY is asymptomatic and, although it is autosomal dominantly inherited, there may be no known family history of diabetes. Testing of apparently unaffected parents can reveal that one parent has mildly raised fasting plasma glucose.

Differentiating from type 1 and 2 diabetes

Diagnosis of glucokinase MODY is most important in young patients who may otherwise be thought to have T1DM and treated with insulin [15]. Unlike T1DM, hyperglycemia remains mild, β-cell antibodies are usually negative and (if tested) one parent is likely to have mild hyperglycemia. Fasting C-peptide will remain detectable and the post meal rise in glucose concentration will be far less than in T1DM. Differentiating glucokinase MODY from T2DM can be more difficult as both conditions can cause mild hyperglycemia with a strong family history. Lack of obesity and features of insulin resistance, a small increment on oral glucose tolerance testing and non-progression all suggest glucokinase MODY.

Management

Outside of pregnancy, hypoglycemic medication is not recommended as hyperglycemia is mild, complications are rare and medication appears to have minimal effect because the regulation of glycemia is preserved [16]. Once diagnosis is confirmed, treatment can usually be discontinued; however, this should be done with caution as it is possible for T1DM or T2DM to coexist with a *GCK* mutation.

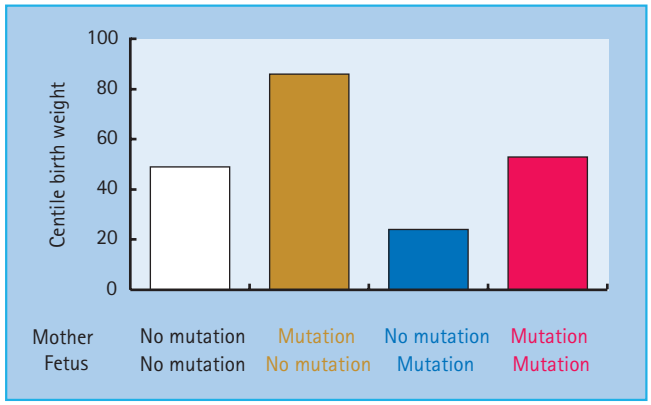

Figure 15.5 The centile birth weight of children in families with glucokinase mutations. The weight is increased by the presence of a maternal mutation and decreased by the presence of a fetal mutation. Data from Hattersley *et al.* [18].

Glucokinase MODY and pregnancy

Clinical features

Patients with *GCK* mutations are frequently found to have hyperglycemia during screening in pregnancy and represent approximately 3% of Caucasian patients with gestational diabetes [17]. Their identification is important because they have a different clinical course, both within and outside pregnancy, than other subjects with gestational diabetes. The birth weight of the newborn infant will depend on the mutation status of both the mother and the fetus (Figure 15.5). Where only the mother carries the mutation, maternal hyperglycemia may result in increased fetal insulin secretion and growth causing the fetus to be large for gestational age [18]. If the fetus inherits the mutation from the father, however, birth weight is reduced by approximately 500 g as a result of reduced fetal insulin secretion and insulin-mediated fetal growth [18]. If both mother and fetus have the *GCK* mutation the two opposing effects are cancelled out and the newborn infant is of normal weight.

Genetic testing for *GCK* mutations in pregnancy

We recommend testing for *GCK* mutations when a pregnant patient is found to have persistently raised fasting plasma glucose 5.5–8 mmol/L and an increment of <4.6 mmol/L on at least one oral glucose tolerance test (either during or outside pregnancy). An absence of family history should not exclude the diagnosis as asymptomatic hyperglycemia in a parent may not have been detected.

Management

Patients with hyperglycemia resulting from glucokinase mutations are often treated with insulin during pregnancy in an attempt to correct the fasting hyperglycemia. Fetal genotype, however, is a far greater determinant of fetal birth weight than treatment of the mother and insulin treatment appears to have little effect on fetal growth [19]. This probably reflects the difficulty in lowering the blood glucose in glucokinase patients because of increased counter-regulation [20]. Patients stop producing their own insulin and produce counter-regulatory hormones if blood glucose is reduced to normal levels, making successful control of blood glucose with insulin difficult. This results in frequent hypoglycemic symptoms at non-hypoglycemic blood sugar levels and means that large doses of insulin may be required to reduce fasting hyperglycemia to normal levels [20,21]. In some cases where the fetus has inherited the mutation, intensive insulin treatment has resulted in a low birth weight child [21]. This is to be expected as a small baby is seen when the fetus inherits a mutation from the father and is born to a normoglycemic mother [18,22]. Testing fetal genotype *in utero* is not without risk. Treatment decisions in glucokinase gestational diabetes should therefore be related to fetal growth as shown by scans rather than being made solely on maternal glycemia [21]. If the abdominal circumference is greater than the 75th centile insulin may be used but early delivery is the most successful strategy.

HNF1A and *HNF4A* (transcription factor MODY)

Transcription factors are proteins that bind to DNA and form part of a complex regulatory network controlling gene expression. The majority of patients with MODY have a heterozygous mutation in a transcription factor gene, by far the most common being mutations in the hepatic nuclear factors 1A and 4A (*HNF1A* and *HNF4A*). Diabetes resulting from mutations in other transcription factor encoding genes including *HNF1B*, insulin promoter factor 1 (IPF-1) and *NEUROD1* are discussed elsewhere in this chapter.

Transcription factor mutations alter insulin secretion in the mature β-cell as well as altering β-cell development, proliferation and cell death. Mutations in the hepatic nuclear factors appear to alter levels of proteins critical in metabolism including the GLUT-2 glucose transporter and key enzymes in the mitochondrial metabolism of glucose [23–25]. Reduced β-cell proliferation and preserved or increased apoptosis could explain the progressive deterioration in β-cell function seen in these patients [25–28].

Mutations in *HNF1A* account for up to 70% of cases of MODY with nearly 200 different mutations reported. *HNF4A*, the next most common, accounts for approximately 3% of cases [29].

Clinical features

Heterozygous transcription factor mutations cause autosomal dominant diabetes presenting in adolescence or early adulthood resulting from progressive failure of insulin secretion. While diabetes is similar in *HNF1A* and *HNF4A* mutation carriers as a result of a common pattern of β-cell dysfunction, a number of differences in extrapancreatic features occur (Table 15.3).

Diabetes

Patients are usually born with normal glucose tolerance and then show progressive β-cell dysfunction until they develop diabetes,

Table 15.3 Extrapancreatic features assisting in the differential diagnosis of transcription factor maturity-onset diabetes of the young (MODY).

Transcription factor	Extrapancreatic clinical features
HNF1A	Low renal glucose threshold (glycosuria) Raised HDL Raised cardiovascular risk (in excess of type 2 diabetes)
HNF4A	Increased birth weight/macrosomia Low HDL, low lipoprotein A1 and A2, raised LDL
HNF1B	Renal cysts and renal development disorders and multiple others. See Table 15.5
NeuroD1	None described

HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

usually between 10 and 30 years of age (Figure 15.4). Sixty-three percent of *HNF1A* carriers are diagnosed with diabetes by the age of 25 years and 79% by the age of 35 years; the age of diagnosis is partly related to the location of the underlying mutation within the gene [30–32]. Patients show deteriorating glycemia with age and require pharmacologic treatment. In the oral glucose tolerance test, in contrast to patients with glucokinase mutations, the fasting glucose is often normal initially but there is marked elevation of glycemia at 2 hours and consequently a large 2-hour increment (>5.0 mmol/L) [13]. This occurs because insulin secretion rates in early *HNF1A* MODY remain appropriate, with blood glucose values less than 8.0 mmol/L but are reduced significantly in comparison to non-diabetic non-mutation carriers above this level [33]. Microvascular complications are frequent particularly when hyperglycemia is inadequately treated [34]. Patients tend to be lean and insulin-sensitive. Obesity occurs at similar levels to the normal population.

Extrapancreatic clinical features

These are summarized in Table 15.3 and discussed in more detail below.

HNF1A

Patients with *HNF1A* mutations have elevated levels of high density lipoprotein cholesterol (HDL) which contrasts with the reduced HDL levels seen in T2DM [35]. Despite this they appear to have a greater risk of coronary heart disease than patients with T1DM [34]. Frequency of microvascular complications is similar to that seen in T1DM and T2DM and relates to degree of glycemic control [34]. Patients have a reduced renal threshold for glucose. Mutation carriers without diabetes may develop glycosuria after a glucose challenge even if glycemia remains within normal limits [36].

HNF4A

HNF4A mutations are associated with an 800 g increase in birth weight compared with non-mutation carrying siblings [37]. This means the offspring of *HNF4A* mutation carrying fathers, as well as the offspring of *HNF4A* mothers, are at risk of marked macrosomia. There is also an increased risk of hypoglycemia in affected neonates. These features appear to relate to increased insulin secretion *in utero* and in early infancy which evolves into reduced insulin secretion and diabetes in later life [37]. *HNF4A* mutation carriers have reduced levels of HDL (and lipoprotein A1 and A2) and frequently have raised LDL, while triglyceride levels are similar to population norms [38].

Differentiating from type 1 diabetes

These patients are usually diagnosed as having T1DM as they have symptomatic diabetes occurring in adolescence or young adulthood. We recommend genetic testing for *HNF1A* mutations in any young adult with apparent T1DM, a parent with diabetes, and who is antibody-negative at diagnosis. Evidence of non-insulin dependence increases the likelihood of a positive result; this would include no ketosis in the absence of insulin treatment, good glycemic control on low doses of insulin, or detectable C peptide with plasma glucose >8 mmol/L 3–5 years after diagnosis (outside the honeymoon period) [39]. While glutamine acid decarboxylase (GAD) antibodies are usually negative, positive GAD antibodies may be expected in up to 1–2% of the non-diabetic normal population, and therefore positive antibodies (particularly at low titer) may not exclude monogenic diabetes; testing should be considered where clinical suspicion is high [40,41]. *HNF4A* testing should be performed in any patient with a high suspicion of having *HNF1A* who tests negative for *HNF1A* mutations, particularly where there is evidence of increased birth weight and/or neonatal hypoglycemia.

Differentiating from type 2 diabetes

HNF1A should be suspected and mutation screening performed in patients otherwise suspected to be have T2DM where the following features are present ([39] and www.diabetesgenes.org):

1 Young-onset diabetes – typically before 25 years old in at least one family member;

2 Family history of diabetes – at least two generations and ideally two individuals diagnosed in their twenties or thirties), particularly where affected individuals are non-obese;

3 Absence of obesity, acanthosis nigricans or other evidence of insulin resistance.

In addition, a large increment in the glucose tolerance test (>5 mmol/L), presence of glycosuria with blood glucose less than 10 mmol/L, marked sensitivity to sulfonylureas and a lipid profile showing normal or raised HDL and normal or low triglycerides (atypical for T2DM) would all be supportive of a diagnosis of *HNF1A* instead of T2DM [35]. *HNF4A* should be suspected and tested in those patients who are suspected to have *HNF1A* mutations but test negative on *HNF1A* screening. These patients have a normal renal glucose threshold and frequently have a personal and/or family history of high birth weights and/or neonatal hypoglycemia.

Management

Patients with both *HNF1A* and *HNF4A* mutations are sensitive to sulfonylurea therapy which we recommend as first line treatment [38,42]. Glycemic control with sulfonylureas is often better than with insulin and the fasting glucose lowering effect is 4 times greater than that seen in T2DM [42,43]. Transfer to sulfonylurea treatment is successful in the majority of patients although insulin therapy may be required as diabetes progresses [44]. Even very low sulfonylurea doses may cause hypoglycemia. The starting dose should therefore be low – we use a starting dose of 40 mg/day gliclazide or 2.5 mg/day glibenclamide in adults. If there is hypoglycemia with low doses of standard agents, a short-acting agent such as nateglinide may be appropriate [45]. Because of the apparent increased risk of cardiovascular disease in *HNF1A*, statin therapy should be considered and we suggest it for all patients aged over 40 years.

Management in pregnancy

Evidence to support management strategies for *HNF1A* and *HNF4A* in pregnancy is very limited. Our current practice is to continue sulfonylureas if glycemic control is good before pregnancy but otherwise institute treatment with insulin. Consideration should be given to switching to glibenclamide in the prepregnancy period as this sulfonylurea has the most evidence for safety in pregnancy [46,47]. If a fetus carries *HNF4A*, the risk of macrosomia and neonatal hypoglycemia is high whether the mutation comes from the mother or father [37]. If either parent is known to carry a *HNF4A* mutation, we recommend:

1 Very tight glucose control in mothers with diabetes to attempt to minimize macrosomia;
2 Serial antenatal ultrasound scans to look for macrosomia with early delivery if this is marked; and
3 Early measurement of neonatal glucose and consideration of diazoxide treatment if hypoglycemia persists.

Other transcription factor MODY

Other transcription factor mutations causing autosomal dominant β-cell diabetes have been identified in the genes *IPF1*, *NEUROD1*, *KLF11* and *PAX 4* but all are very rare [48–53].

Neonatal diabetes and diabetes diagnosed within 6 months of life

Children diagnosed with diabetes within the first 6 months of life (referred to as neonatal diabetes) are likely to have monogenic diabetes and not T1DM [54–57]. These patients commonly present with ketoacidosis and absent C-peptide. Neonatal diabetes is rare, affecting 1 in 100 000–200 000 live births [58]. Approximately half of cases remit spontaneously and are therefore termed transient neonatal diabetes mellitus (TNDM) as opposed to permanent neonatal diabetes mellitus (PNDM) where diabetes persists. TNDM often recurs in later life [59]. Neonatal diabetes results from mutations of key genes involved in β-cell development or function. Table 15.4 summarizes the known genetic causes of neonatal diabetes.

Table 15.4 Causes of neonatal diabetes.

Pancreatic pathophysiology	Protein, chromosome or gene affected	Prevalence	Inheritance	Features in addition to neonatal diabetes and low birth weight
Reduced β-cell function	K_{ATP} channel (*KCNJ11* and *ABCC8*)	50% of permanent neonatal diabetes, 25% of transient neonatal diabetes	85% spontaneous. Remainder autosomal dominant or recessive	Developmental delay and epilepsy. Sulfonylurea responsive
	Chromosome 6q24	70% of transient neonatal diabetes	Variable	Macroglossia and umbilical hernia
	Glucokinase (homozygous for mutation)	Rare	Autosomal recessive	Both parents have heterozygous glucokinase associated hyperglycemia
	SLC2A2	Rare	Autosomal dominant	Hypergalactosemia, hepatic failure
	GLIS3	Rare	Autosomal recessive	Congenital hypothyroidism, glaucoma, liver fibrosis and cystic kidney disease
Reduced pancreatic mass	*PTF1A*	Rare	Autosomal recessive	Pancreatic and cerebellar agenesis
	PDX1	Rare	Autosomal recessive	Pancreatic agenesis
	HNF1B	Rare	Autosomal dominant	Exocrine pancreas insufficiency and renal cysts
Increased β-cell destruction	*EIF2AK3*	Rare	Autosomal recessive	Spondyloepiphyseal dysplasia, renal failure, recurrent hepatitis and mental retardation
	FOXP3	Rare	X-linked	Immune dysregulation, intractable diarrhoea, eczematous skin rash and elevated IgE
	INS	12% of permanent neonatal diabetes	Autosomal dominant	None

Permanent neonatal diabetes

Approximately half of PNDM is caused by mutations in the genes *KCNJ11* and *ABCC8* which encode the Kir6.2 and SUR1 subunits, respectively, of the β-cell ATP-sensitive potassium channel (K_{ATP} channel) [60–63]. This channel is constitutively open and regulates insulin secretion by closing in response to the raised intracellular ATP levels that occur as a consequence of hyperglycemia. Channel closure triggers depolarization of the β-cell membrane which leads to insulin secretion. Activating mutations in *KCNJ11* and *ABCC8* prevent closure of the potassium channel in response to increased ATP so the β-cell remains hyperpolarized and unable to secrete insulin [64]. Sulfonylureas close the β-cell K_{ATP} channel by an ATP independent route and they have been used successfully in the management of the majority of patients with neonatal diabetes resulting from *KCNJ11* and *ABCC8* mutations [65]. The K_{ATP} channel is also present in the brain, nerves and muscles. Reflecting this distribution of channels, 20% of patients with *KCNJ11* mutations (and occasional patients with *ABCC8* mutations) have associated neurologic features [57,60,61,64].

Heterozygous mutations in the insulin gene (*INS*) have been identified in 12% of cases of isolated PNDM and insulin treatment is required [66,67]. A number of other genetic causes have been found which all appear to be relatively rare [58] as outlined in Table 15.4.

The majority (85%) of PNDM resulting from K_{ATP} channel mutations arise spontaneously from *de novo* heterozygous mutations, with the remainder being familial and inherited mainly in an autosomal dominant pattern. About 40% of neonatal diabetes resulting from *ABCC8* mutations, however, are inherited in an autosomal recessive fashion [63].

Clinical features

Diabetes caused by *KCNJ11* mutations typically present in the first 26 weeks of life (median 4–6 weeks) with marked hyperglycemia often accompanied by ketosis. C-peptide is usually undetectable and islet cell antibodies negative [60]. As with all neonatal diabetes subtypes, infants are often small for gestational age as a result of reduced fetal insulin secretion with consequent decreased insulin mediated growth. About 20% of patients with PNDM and *KCNJ11* mutations have neurologic features, the most common being developmental delay, sometimes with muscle weakness and/or epilepsy. The most severe form where neonatal diabetes is accompanied by developmental delay and epilepsy has been named developmental delay, epilepsy and neonatal diabetes (DEND). "Intermediate DEND" refers to neonatal diabetes with less severe developmental delay and no epilepsy. The severity of the clinical condition relates closely to the underlying mutation and its effect on K_{ATP} channel ATP sensitivity [64,68].

Neonatal diabetes caused by *ABCC8* mutation has a similar phenotype but leads to transient neonatal diabetes more commonly than PNDM and has associated neurologic features only rarely [61–63]. Patients with neonatal diabetes and *INS* mutations present at a median age of 9 weeks and are also often small for gestational age but do not have extrapancreatic features [66].

Management

Although insulin therapy is commonly used in the initial period after diagnosis, the majority of patients with *KCNJ11* and *ABCC8* mutations can successfully transfer from insulin to sulfonylurea therapy, usually with significant improvements in glycemic control [62,65]. Ninety percent of those with *KCNJ11* mutations are able to discontinue insulin, while HbA_{1c} appears to improve in all patients with a mean drop from 65 to 46 mmol/mol (8.1 to 6.4%) after 12 weeks [65]. Glibenclamide was initially selected as it is non-selective and widely available; it has been used in the majority of cases and may be more effective than other sulfonylurea agents [69]. The doses needed are often higher than those needed for the treatment of T2DM: a median dose of 0.45 mg/kg/day is required with doses up to 1.5 mg/kg/day needed in some cases [65,70]. Diarrhoea is a possible side effect but this usually only lasts 1–3 days [71]. Sulfonylurea therapy may result in some improvement in neurologic features even where they are commenced in adulthood [69,72,73]. Further information on transferring patients from insulin to sulfonylureas can be found at www.diabetesgenes.org.

Neonatal diabetes resulting from *INS* mutations requires insulin treatment [66]. Affected individuals with a heterozygous *KCNJ11* mutation contemplating parenthood should be counseled that they have a 50% chance of passing on the mutation to their offspring. Where unaffected parents whose child is affected by a heterozygous mutation are planning further pregnancies, the risk of further affected children is low because of the possibility of a germline mutation is approximately 5–10% [74]. Where parents have a child with neonatal diabetes caused by a recessive *ABCC8* mutation, there is a 25% chance of each further offspring being affected but the risk is low for subsequent generations.

Transient neonatal diabetes

The genetic etiology of more than 90% of transient neonatal diabetes has been established. The majority (70%) of cases result from abnormalities the q24 region of chromosome 6 (6q24) affecting imprinted genes [58,75]. Genetic imprinting occurs when only the maternal or paternally inherited allele of a gene is expressed. In TNDM paternal uniparental disomy, paternal duplication of 6q24 or abnormal methylation of the maternal copy of the chromosome causes overexpression of the paternal copies of the genes *PLAGL1* (also known as *ZAC*) and *HYMAI* [75,76]. Paternal duplication of 6q24 can be inherited, therefore this abnormality causes the majority of inherited TNDM cases. Uniparental disomy causes sporadic TNDM; cases resulting from abnormal methylation of the maternal copy of chromosome 6 may be sporadic or inherited [75,76]. The majority (90%) of TNDM not associated with 6q24 abnormalities are caused by mutations in *KCNJ11* and *ABCC8* [57,59,62,77–81].

Clinical features

6q24 diabetes usually presents in the first week of life often with severe hyperglycemia and dehydration but usually without ketosis

[75]. Islet cell antibodies are usually negative and C-peptide is low or negligible [75]. Low birth weight is common (mean birth weight 2.1 kg), and there may be associated macroglossia and/or umbilical hernia. Insulin treatment is required for a median of 12 weeks before the patient goes into remission. Diabetes recurs later in life in 50–60% of patients as a result of β-cell dysfunction. The average age of recurrence is 14 years. In some cases hyperglycemia may be intermittent and seen only at times of stress [75,82]. Where TNDM is caused by *KCNJ11* and *ABCC8* mutations, diabetes tends to present later (median 4 weeks), takes longer to remit and is associated with less intrauterine growth restriction (median birth weight 2.6 kg) [59].

Management

Insulin is required in the neonatal period whereas treatment requirements following relapse vary from diet to oral hypoglycemics or insulin [82]. In TNDM cases resulting from *KCNJ11* and *ABCC8* mutations, diabetes may be successfully managed with sulfonylureas [59,62].

Genetic counseling depends on the underlying genetic etiology. Cases caused by uniparental disomy are sporadic and therefore have low risk of occurrence in either siblings or offspring of the affected child. Methylation defects often result from homozygous mutations in the transcription factor gene *ZFP57* and therefore may be inherited in an autosomal recessive manner [76]. Offspring of males with 6q24 duplication have a 50% chance of developing TNDM whereas if the abnormality is inherited from the mother they will not be affected but the TNDM may occur in the following generation [82].

Genetic testing in neonatal diabetes

At the time of diagnosis of neonatal diabetes it is not known whether the diabetes will be transient or permanent. We recommend testing for 6q24 abnormalities, *KCNJ11*, *ABCC8* and *INS* mutations at diagnosis in all diabetes diagnosed before 6 months. Identifying mutations in these genes is important as it will influence treatment. An early diagnosis and very low birth weight make 6q24 most likely. A genetic cause (*KCNJ11* or *INS*) can be established in approximately 7% of diabetes diagnosed between 6 months and 1 year of age so consideration should be given to testing this age group, especially where autoantibody tests are negative [56].

Diabetes with extrapancreatic features

A number of monogenic causes of diabetes are associated with distinct features occurring outside the pancreas. In many cases extrapancreatic disease may be the presenting feature, for example in cystic fibrosis and hemochromatosis (see Chapter 18). Clinical subtypes and management of monogenic β-cell diabetes that have extrapancreatic features are summarized in Figure 15.6.

Maternally inherited diabetes and deafness

Maternally inherited diabetes and deafness (MIDD) results from a mutation in mitochondrial DNA and causes maternally inherited diabetes with sensorineural deafness that may be accompanied by a wide range of other features. It affects up to 1% of patients with diabetes but is frequently undiagnosed [83].

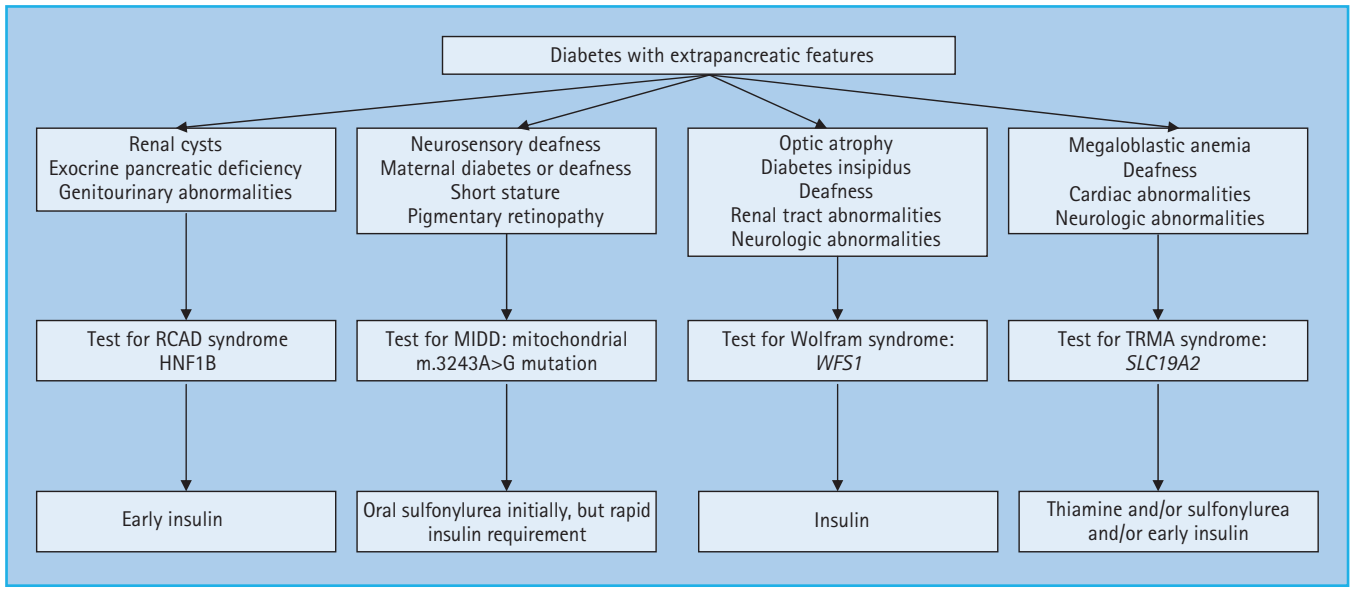

Figure 15.6 Clinical subtypes and management of monogenic β-cell diabetes that has extrapancreatic features. *HNF1B*, hepatocyte nuclear factor 1B; MIDD, maternally inherited diabetes and deafness; RCAD, renal cysts and diabetes; *SLC19A2*, solute carrier family 19, member 2 gene; TRMA, thiamine responsive megaloblastic anemia; *WFS1*, Wolfram syndrome 1 gene.

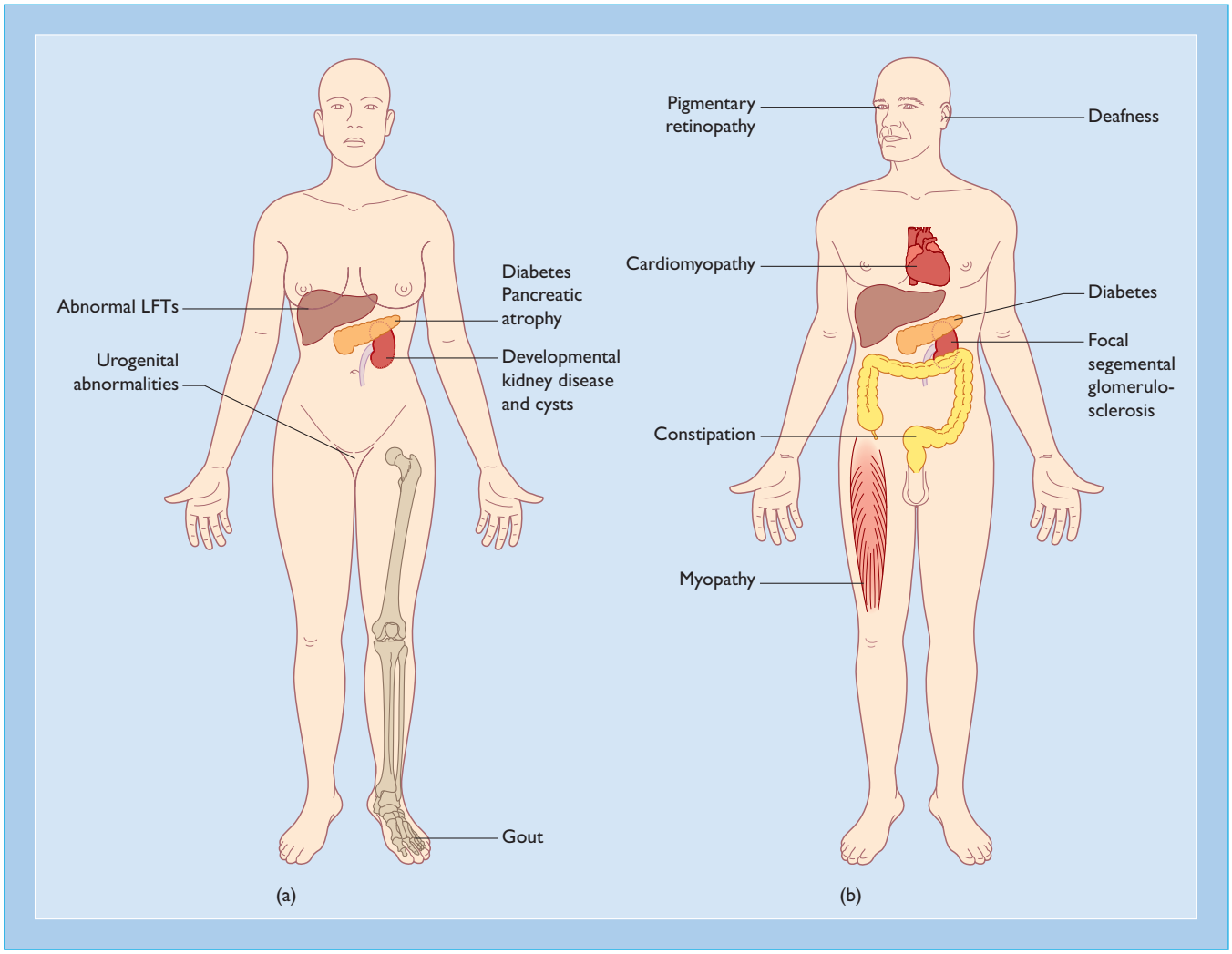

Figure 15.7 Phenotypes of: (a) renal cysts and diabetes syndrome due to *HNF1B* mutation or deletion; (b) maternally inherited diabetes and deafness caused by mitochondrial m.3243A>G mutation. Adapted from Murphy *et al.* [181].

Pathogenesis

The vast majority of mitochondrial diabetes results from the m.3243A>G point mutation in mitochondrial DNA. Other mitochondrial DNA mutations have been implicated but are rare [84].

The m.3243A>G mutation affects the mitochondrial respiratory chain and therefore may result in cellular energy deficiency. Organs that are most affected are those with high metabolic activity which include the endocrine pancreas, cochlea and in some cases the retina, muscle, kidney and brain. Mitochondrial dysfunction in pancreatic islets results in abnormal β-cell function, loss of β-cell mass and insulin deficiency while insulin sensitivity is usually normal although can be reduced (reviewed in [83]). As mitochondria are only inherited from the mother, the maternal line in a family is affected, and children of a male patient are not at risk. Although all children of an affected female are likely to carry the mutation, phenotype can vary widely in the same family because of heteroplasmy. Offspring inherit a mix of mutant and wild-type mitochondrial DNA – the proportion of mitochondria carrying the mutation will vary in offspring of an affected mother as will subsequent segregation of mitochondria to different tissues.

Clinical features

The characteristic clinical features of MIDD are summarized in Figure 15.7. The majority of mutation carriers develop diabetes (over 85%) and sensorineural hearing loss (over 75%) [85–88]. There is usually a family history of diabetes and/or hearing loss in maternal relatives but clinical features can vary greatly even within the same pedigree [89]. Diabetes is progressive and usually presents with insidious onset similar to T2DM but may present acutely, with ketoacidosis occurring in approximately 8% of cases [85,86,90]. Mean age at diagnosis of diabetes is 37 years but age of diagnosis can range from early adolescence to old age [86,90,91].

Hearing loss typically develops in early adulthood but again may occur in children as well as the elderly; it is more common and often more severe in men [86,88]. Patients with the m.3243A>G mutation have a high prevalence of renal failure with focal segmental glomerular sclerosis (FSGS) found more frequently than diabetic nephropathy on renal biopsy [86,92]. Diabetic retinopathy may be less prevalent than in other forms of diabetes; macular retinal dystrophy is frequent but rarely causes visual symptoms [83,86,92]. Cardiac abnormalities include left ventricular hypertrophy, heart failure (which can progress rapidly), cardiac autonomic neuropathy and cardiac arrhythmias [93–97]. Other possible clinical manifestations of the m.3243A>G mutation include short stature, MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), psychiatric disorders, proximal myopathy and gastrointestinal symptoms [83].

Differentiating from type 1 and 2 diabetes

Diabetes caused by the m.3243A>G mutation may present like T1DM or T2DM [85,86,90]. GAD antibodies are usually but not always negative [98–100]. The presence of deafness in the patient or clustering of diabetes and/or deafness in maternal relatives should prompt investigation for the m.3243A>G mutation. Short stature, early-onset cardiomyopathy, myopathy, early-onset stroke or macular retinal dystrophy on retinal screening may all raise suspicion of MIDD [83].

If there is clinical suspicion of MIDD, the diagnosis can be confirmed by testing for the m.3243A>G mutation, usually in blood leukocytes. In rare cases the result may be negative on blood-derived DNA testing despite the presence of the mutation in other tissues as a result of heteroplasmy. Testing of other samples (e.g. urine or mouthwash) may be more appropriate than blood [83].

Management

Diabetes usually requires early insulin treatment (mean 2 years post diagnosis) [85,86,90,100]. There is a theoretical basis for avoiding metformin in view of the risk of lactic acidosis [83,85]. There may be some benefit in co-enzyme Q10 supplementation although randomized double-blind control trials have yet to be performed [101,102]. Monitoring for cardiac manifestations should be considered from a young age, particularly if there are clinical features or family history of early cardiomyopathy. Aggressive blood pressure management and early angiotensin-converting enzyme (ACE) inhibitor treatment may be appropriate in view of the high risk of renal complications. Renal biopsy to exclude FSGS may be necessary in those who develop renal failure [83]. Management of hearing loss involves avoidance of exacerbating factors, prompt treatment of ear infections, hearing aids if necessary and consideration of cochlear implants where there is profound hearing loss [83,103,104].

Maternal relatives of affected patients and children of female patients should be assumed to carry the m.3243A>G mutation. Therefore, periodic screening for the features and complications of MIDD may be advisable. In contrast, paternal relatives and children of an affected male are not at risk of carrying the mutation.

Renal cysts and diabetes (*HNF1B* MODY)

HNF1B is a transcription factor with a role in regulating gene expression in a number of tissues including the pancreas, kidneys, liver genital tract and gut [105]. Heterozygous deletions or mutations in *HNF1B* can cause developmental abnormalities in all these organs although the most common phenotypes are renal abnormalities and diabetes. *HNF1B* abnormalities may show autosomal dominant inheritance, although 32–58% of cases arise spontaneously and there is a wide variation in phenotype even with identical mutations [106–110].

Clinical features

The clinical features are summarized in Table 15.5 and Figure 15.7. Developmental renal disease is the most consistent feature with renal cysts being the most common manifestation [106]. Other possible renal abnormalities include glomerulocystic kidney disease, cystic renal dysplasia and morphologic abnormalities such as horseshoe kidney. Renal function can range from

Table 15.5 Features of patients with *HNF1B* mutations causing RCAD (renal cysts and diabetes) in a UK cohort. Adapted from Bingham & Hattersley [108].

Clinical features	Subjects with *HNF1B* mutations and details (%)
Renal phenotype	
Renal cysts	66%
Renal impairment	86% (15% dialysis/transplantation)
Morphologic renal abnormalities	Horseshoe kidney Single kidney
Renal histology (includes)	Glomerulocystic kidney disease Cystic renal dysplasia Oligomeganephronia
Diabetes	58% Mean age of diagnosis 26 years, range 10–61 years Insulin treatment common
Other features	
Hypomagnesemia	40%
Short stature	20% <2 SD below mean height
Hyperuricemia and gout	20% (clinical gout)
Uterine abnormalities	17%
Hypospadias	17%
Joint laxity	Rare
Hearing loss	Rare
Prognathism	Rare
Pyloric stenosis	Rare
Learning difficulties	Rare
Chromophobe renal cell carcinoma	Rare

normal to dialysis dependent [111,112]. Half of *HNF1B* mutations carriers have early-onset diabetes caused by both insulin deficiency as a result of reduced β-cell number and increased hepatic insulin resistance. The sensitivity to sulfonylureas found with *HNF1A* and *HNF4A* mutations is absent [113]. Diabetes is usually associated with pancreatic hypoplasia and may be associated with exocrine dysfunction although this is rarely symptomatic [114–116]. Low birth weight is common and transient neonatal diabetes may occur [115]. Other clinical manifestations include abnormal liver function tests, genital tract malformations, hypomagnesemia, hyperuricemia and familial hyperuricemic nephropathy [114,117]. An association with chromophobe renal cell carcinoma has been reported reflecting a probable role for *HNF1B* as a tumour suppressor gene [118,119].

Differentiating from type 1 and 2 diabetes

Approximately 50% of *HNF1B* mutations and deletions are spontaneous and so patients may not have a family history. Testing for *HNF1B* abnormalities should be considered where there is unexplained cystic renal disease, glomerulocystic disease or other renal developmental abnormalities with or without a past medical or family history of diabetes. It should also be considered in individuals with genital tract abnormalities associated with renal abnormalities. Both simple renal cysts and diabetes are common in the general population and should not lead to testing for *HNF1B* abnormalities. Testing for *HNF1B* should always include dosage analysis to detect gene deletions as these are common and will be missed if the laboratory performs sequencing only [120].

Management

Early insulin therapy is usually required for management of diabetes. The sulfonylurea sensitivity seen in other transcription factor diabetes is not seen in *HNF1B*. Renal management is similar to management of other chronic progressive renal diseases. Our recommendation is to repeat renal ultrasound imaging every 2 years in view of the possible increased risk of chromophobe renal carcinoma and to screen for diabetes yearly in non-diabetic mutation carriers.

Other monogenic β-cell diabetes with extrapancreatic features

Wolfram syndrome

Wolfram syndrome (also known as DIDMOAD [diabetes insipidus, diabetes mellitus, optic atrophy and deafness]) is a rare recessive neurodegenerative disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy deafness and a variety of central nervous system abnormalities. Consideration should be given to this diagnosis where there is a combination of diabetes and optic atrophy [121,122].

Thiamine responsive megaloblastic anemia

Thiamine responsive megaloblastic anemia is a rare autosomal recessive condition characterized by megaloblastic anemia (which may be mild), non-autoimmune diabetes mellitus and sensorineural hearing loss. Treatment with high dose thiamine can improve some features including diabetes [123].

Wolcott–Rallison syndrome

Wolcott–Rallison syndrome is a rare autosomal recessive condition characterized by early-onset diabetes, spondyloepiphyseal dysplasia, acute hepatic failure, renal impairment and developmental delay. Diabetes usually presents in infancy and requires insulin treatment [124].

Monogenic diabetes with pancreatic exocrine dysfunction

Mutations in the carboxyl ester lipase (*CEL*) gene have recently been identified as a rare cause of monogenic diabetes with pancreatic exocrine dysfunction [125].

Insulin resistance

Monogenic causes of diabetes resulting from insulin resistance include the inherited lipodystrophies, mutations affecting the insulin receptor or post receptor signaling and other monogenic syndromes associated with insulin resistance where abnormalities of insulin action are not the primary disorder. There can be considerable clinical overlap in clinical presentation between these conditions [126]. The presence of acanthosis (Figure 15.8) in a thin patient with diabetes should prompt consideration of underlying monogenic causes of insulin resistance.

Insulin receptor gene mutations

Insulin exerts its effects through binding to a transmembrane receptor, consisting of two alfa and two beta subunits, present on the surface of target cells. Binding of insulin to the alfa subunit activates beta subunit tyrosine kinase activity triggering protein

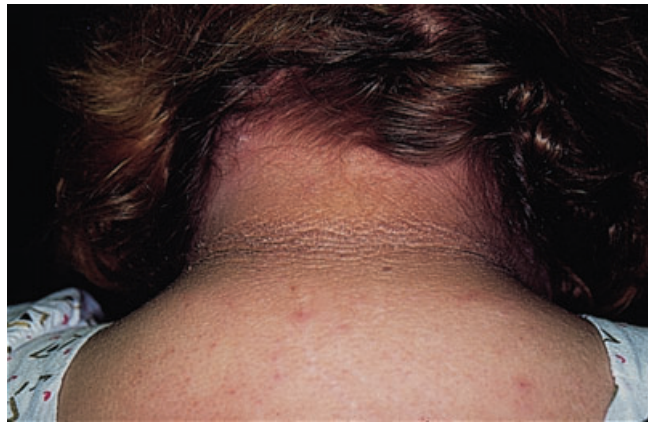

Figure 15.8 Acanthosis nigricans affecting the neck of a 26-year-old woman with severe insulin resistance. Reproduced from Moller & O'Rahilly [182] with permission.

activation cascades which lead to insulin's intracellular effects [127,128]. Mutations in the insulin receptor gene lead to inherited insulin resistance syndromes. The severity of the resulting clinical phenotype depends on the extent of impairment of signal transduction resulting from the underlying mutation [129].

Clinical features

Individuals with severe insulin resistance resulting from insulin receptor mutations may have a number of common features including hyperinsulinemia, acanthosis nigricans, ovarian hyperandrogenism and disturbances of glucose homeostasis which can include hypoglycemia as well as impaired glucose tolerance and diabetes [129]. Three main syndromes resulting from insulin receptor mutations resulting in severe insulin resistance have been described: Type A insulin resistance syndrome, Rabson–Mendenhall syndrome and leprechaunism (Donohue syndrome). There may be considerable clinical overlap and these syndromes may simply represent varying clinical features from a continuum of severity of receptor dysfunction rather than completely distinct syndromes [129]. Many patients with insulin receptor defects and severe insulin resistance (adult males in particular) may not fit into the syndromic descriptions below.

Features of the Type A insulin resistance syndrome include severe insulin resistance, acanthosis nigricans, polycystic ovarian disease, hirsutism and signs of virilization occurring in young females (often termed HAIR-AN syndrome). The patients with an underlying insulin receptor mutation are usually slim [130,131]. The most severe syndrome seen with insulin receptor mutations is leprechaunism (Donohue syndrome), a rare autosomal recessive disorder in which patients have low birth weight, growth restriction, disordered glucose homeostasis, characteristic dysmorphic features and usually do not survive infancy [131,132].

Rabson–Mendenhall syndrome is an autosomal recessive disorder that is between leprechaunism and Type A insulin resistance in terms of the severity of insulin resistance. Patients present in childhood with acanthosis nigricans, extreme growth retardation, dysplastic dentition, coarse facial features, lack of subcutaneous fat and pineal hyperplasia [131,133,135]. Reported renal abnormalities include medullary sponge kidney and nephrocalcinosis [133,135]. Patients may have paradoxical fasting hypoglycemia at diagnosis but develop frank diabetes (occasionally with ketoacidosis) in later years [134]. Life expectancy is markedly reduced, early death often occurring from complications of diabetes or intractable ketoacidosis.

Differentiating from type 1 and 2 diabetes

The presence of features of insulin resistance in a thin but not an obese individual is suggestive of an underlying insulin receptor gene mutation. Serum adiponectin levels are typically high in patients with insulin receptor mutations whereas they are low in other forms of insulin resistance. It has been suggested that adiponectin levels could be used as a screening test with sequencing of the insulin receptor gene reserved for those case where adiponectin levels are raised [126,136,137].

Unlike T2DM and the lipodystrophies, triglyceride levels in patients with insulin resistance caused by insulin receptor mutations are typically normal [131].

Management

While insulin sensitizers such as metformin and the thiazolidinediones may have a role in management their effect is often limited and insulin therapy is required as β-cell function declines [131]. Glycemic control is often poor despite very high doses of insulin (doses in excess of 500 units/kg/day have been reported). U500 insulin has a role in reducing the insulin volumes required [131,138]. Insulin-like growth factor I (IGF-I) is capable of stimulating glucose uptake and glycogen storage *in vivo* and has therefore been used in treatment of diabetes caused by insulin receptor mutations. Side effects were frequent in early studies but tolerability may be increased by combining IGF-I with its principal binding protein IGFBP-3 [139].

Inherited lipodystrophies

Lipodystrophies are clinically heterogenous disorders that are characterized by the selective loss of adipose tissue. They are associated with insulin resistance and other features such as diabetes mellitus, acanthosis, dyslipidemia, hepatic steatosis and (in female patients) hyperandrogenism, oligomenorrhoea and polycystic ovaries [140]. Lipodystrophies may be inherited or acquired. The inherited subtypes (all of which are rare) are described below.

Famililial partial lipodystrophy

Familial partial lipodystrophies are autosomal dominant disorders associated with the loss of peripheral subcutaneous fat. The two main subtypes result from mutations in *LMNA* and *PPARG*.

Familial partial lipodystrophy associated with *LMNA* mutations (also known as Dunnigan lipodystrophy) results in gradual peripheral subcutaneous fat loss from puberty. This, and the associated muscle hypertrophy, gives a muscular appearance of the arms and legs (Figure 15.9). There may be fat loss from the anterior abdomen and chest and excess fat deposition in the face, neck and intrabdominally [141,142]. Diabetes is common, particularly in female patients [143]. Hypertriglyceridemia may be marked and associated with pancreatitis. Acanthosis and polycystic ovarian syndrome are relatively uncommon. Although hepatic steatosis may develop cirrhosis appears rare [144,145]. Cardiovascular mortality is high.

Familial partial lipodystrophy associated with *PPARG* mutations appears to be phenotypically similar to that caused by *LMNA* mutations although hypertension is more common [146–155].

Diagnosis may be obvious in women but more difficult in males where a muscular appearance of limbs is more common. Early-onset diabetes in a non-obese patient with hypertriglyceridemia should raise suspicion of lipodystrophy particularly if there is marked peripheral fat loss [156].

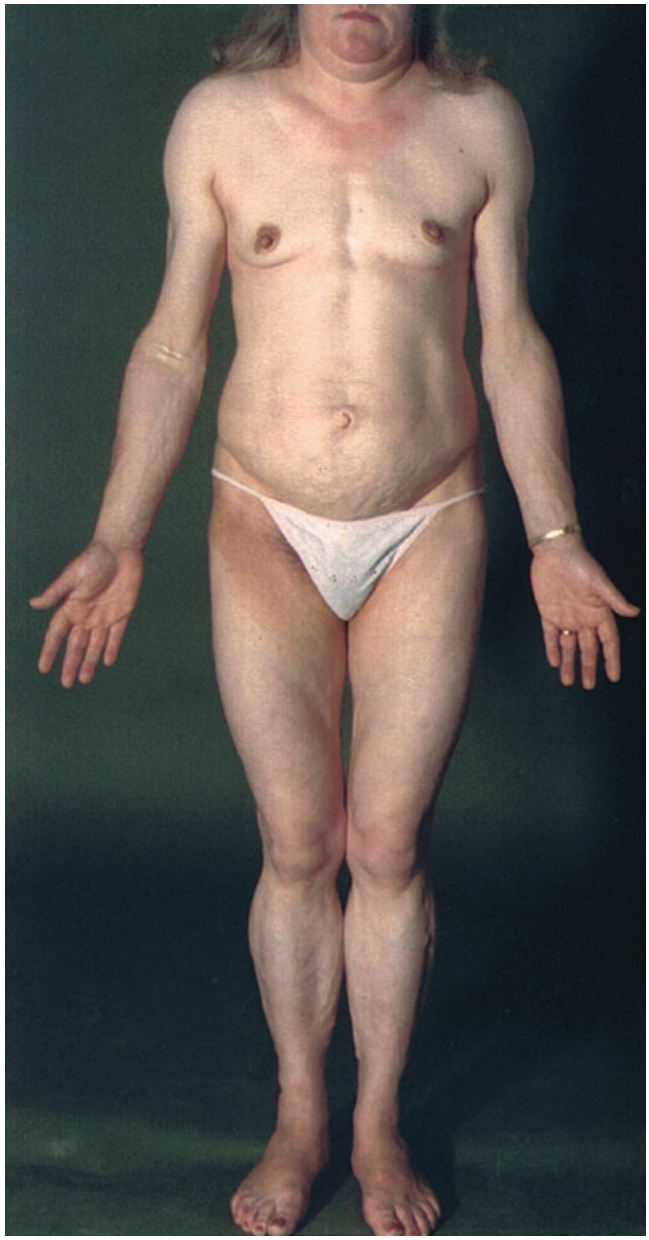

Figure 15.9 Familial partial lipodystrophy in a 46-year-old woman. There is truncal and limb lipodystrophy, preserved facial and neck adipose tissue, muscle hypertrophy and acanthosis apparent in the groin regions.

Congenital generalized lipodystrophy (Berardinelli–Seip syndrome)

This is a rare (estimated prevalence 1 in 10 million) autosomal recessive disorder characterized by a near complete absence of subcutaneous fat from birth, giving a muscular appearance [140]. Because of the absence of functioning adipocytes, lipids are stored in metabolically active tissues. Those affected have features of severe insulin resistance including often widespread acanthosis, hypertriglyceridemia and low HDL cholesterol [157]. Hepatic steatosis occurs early and may lead to cirrhosis; hepatomegaly is seen frequently [158–160]. Childhood growth is accelerated and bone age advanced. Diabetes commonly develops during adolescence [160]. Other associated features include acromegaloid features, hypertrophic cardiomyopathy, skeletal muscle hypertrophy, bone cysts and intellectual impairment [160]. Serum leptin and adiponectin levels are markedly reduced [161].

Three molecularly distinct forms have been identified: congenital generalized lipodystrophy types 1, 2 and 3 resulting from mutations in 1-acylglycerol 3-phosphate-O-acyltransferase 2 (*AGPAT2*), Berardinelli–Seip congenital lipodystrophy 2 (*BSCL2*) and Caveolin-1 (*CAV1*). *AGPAT2* and *BSCL2* account for the majority of cases and have some difference in phenotype. Some patients with this phenotype do not have mutations in any of these genes and so it is likely there are further genetic etiologies to be discovered [140,162,163].

Other inherited forms of lipodystrophy

Rare subtypes of lipodystrophy associated with dysmorphic features include mandibuloacral dysplasia (lipodystrophy with characteristic skeletal abnormalities), SHORT syndrome (short stature, hyperextensibility of joints, ocular depression, Reiger anomaly, teething delay) and neonatal progeroid syndrome [156].

Management of lipodystrophy

Management should address insulin resistance and the main causes of morbidity and mortality in lipodystrophy which include diabetes and its complications, cardiovascular and cerebrovascular disease, recurrent pancreatitis (as a result of severe hypertriglyceridemia), cirrhosis and psychologic distress related to appearance [140].

Lifestyle changes are important and should include an extremely low fat diet (<15% total energy from fat) and increased physical activity [140]. Hypertriglyceridemia that does not respond to lifestyle changes and control of hyperglycemia may require treatment with fibrates and high doses of fish oils. Estrogen replacement including contraceptive pills may exacerbate hypertriglyceridemia and is best avoided.

Glycemic control requires a combination of oral treatments and high dose insulin in the majority of patients. Metformin is commonly used to improve insulin sensitivity although there are no available trial data in inherited lipodystrophies [156]. Response to thiazolidinediones appears to vary with significant improvements in glycemic control and insulin resistance in some but not in all reported cases [155,164–169]. Where insulin is required dose requirements may be very high and U500 insulin appropriate [138,140]. Where proteinuric renal disease develops the threshold for renal biopsy should be low as non-diabetic renal disease (e.g. membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis) appears to be more common than diabetic nephropathy [170].

Levels of the adipocytokine leptin are markedly reduced in severe lipodystrophies. Leptin replacement has been associated with marked improvements in glycemic control and hypertriglyceridemia in a number of cases of both generalized and partial

inherited lipodystrophy [171–177] and may also improve hepatic steatosis [178,179].

Other monogenic conditions associated with insulin resistance

Other monogenic conditions associated with insulin resistance either have marked obesity (e.g. Alström and Bardet–Biedl syndromes); neurologic disease including myotonic dystrophy and Friedreich ataxia or rapid aging (e.g. Werner syndrome) [180].

Use of diagnostic and predictive molecular testing in monogenic diabetes

Diagnostic testing for the major causes of monogenic diabetes is now widely available. Specific recommendations for the different forms of monogenic diabetes are discussed in the relevant sections of this chapter. As molecular testing remains relatively expensive and time-consuming it is recommended that testing is restricted to those individuals with a moderate to high possibility of a positive result. The molecular genetic testing performed should be guided by the clinical phenotype and also the relative prevalence of mutations within that population. As many of these conditions are familial, the characteristics of other family members should also be considered. There should be some caution, however, as monogenic diabetes can occur in families that also have T1DM or T2DM. For similar reasons the results of molecular testing should be interpreted in the context of the clinical findings. For example, a patient with glucokinase diabetes could also develop T1DM or T2DM.

Where a family member has a confirmed genetic diagnosis, phenotypically unaffected relatives should be tested to assess whether they will be at risk of developing diabetes in the future. Where the main mutation phenotype is diabetes, regular urine or blood testing may be preferable as there is little clear extra benefit from prospective testing. Where families do request predictive testing, they should receive full counseling on the potential benefits and disadvantages and be allowed to make their own decisions on this.

Conclusions

Monogenic diabetes results from single gene changes that affect β-cell function or insulin sensitivity. Correct diagnosis can help define prognosis and the best treatment and allow screening of family members. Diagnostic testing is now widely available and should be considered where presentation is atypical for T1DM or T2DM, where there is an autosomal dominant family history, where there are characteristic associated features and in all cases where diabetes has been diagnosed within the first 6 months of life.

References

1 Tattersall RB. Mild familial diabetes with dominant inheritance. *Q J Med* 1974; **43**:339–357.
2 Tattersall R. Maturity-onset diabetes of the young: a clinical history. *Diabet Med* 1998; **15**:11–14.
3 WHO Study Group, Report of a WHO Consultation. *Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: World Health Organization, 1999.
4 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2008; **31**(Suppl 1):S55–S60.
5 Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med* 2001; **345**:971–980.
6 McCarthy MI, Hattersley AT. Learning from molecular genetics: novel insights arising from the definition of genes for monogenic and type 2 diabetes. *Diabetes* 2008; **57**:2889–2898.
7 Matschinsky F, Liang Y, Kesavan P, Wang L, Froguel P, Velho G, *et al.* Glucokinase as pancreatic beta cell glucose sensor and diabetes gene. *J Clin Invest* 1993; **92**:2092–2098.
8 Byrne MM, Sturis J, Clement K, Vionnet N, Pueyo ME, Stoffel M, *et al.* Insulin secretory abnormalities in subjects with hyperglycemia due to glucokinase mutations. *J Clin Invest* 1994; **93**:1120–1130.
9 Velho G, Petersen KF, Perseghin G, Hwang JH, Rothman DL, Pueyo ME, *et al.* Impaired hepatic glycogen synthesis in glucokinase-deficient (MODY-2) subjects. *J Clin Invest* 1996; **98**:1755–1761.
10 Njolstad PR, Sagen JV, Bjorkhaug L, Odili S, Shehadeh N, Bakry D, *et al.* Permanent neonatal diabetes caused by glucokinase deficiency: inborn error of the glucose-insulin signaling pathway. *Diabetes* 2003; **52**:2854–2860.
11 Glaser B, Kesavan P, Heyman M, Davis E, Cuesta A, Buchs A, *et al.* Familial hyperinsulinism caused by an activating glucokinase mutation. *N Engl J Med* 1998; **338**:226–230.
12 Hattersley AT. Maturity-onset diabetes of the young: clinical heterogeneity explained by genetic heterogeneity. *Diabet Med* 1998; **15**:15–24.
13 Stride A, Vaxillaire M, Tuomi T, Barbetti F, Njolstad PR, Hansen T, *et al.* The genetic abnormality in the beta cell determines the response to an oral glucose load. *Diabetologia* 2002; **45**:427–435.
14 Velho G, Blanche H, Vaxillaire M, Bellanne-Chantelot C, Pardini VC, Timsit J, *et al.* Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families. *Diabetologia* 1997; **40**:217–224.
15 Schnyder S, Mullis PE, Ellard S, Hattersley AT, Fluck CE. Genetic testing for glucokinase mutations in clinically selected patients with MODY: a worthwhile investment. *Swiss Med Wkly* 2005; **135**:352–356.
16 Gill-Carey O SB, Colclough K, Ellard S, Hattersley AT. Finding a glucokinase mutation alters patient treatment. *Diabet Med* 2007; **24**(Suppl 1):6.
17 Ellard S, Beards F, Allen LI, Shepherd M, Ballantyne E, Harvey R, *et al.* A high prevalence of glucokinase mutations in gestational diabetic subjects selected by clinical criteria. *Diabetologia* 2000; **43**:250–253.
18 Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S. Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat Genet* 1998; **19**:268–270.

19 Spyer G, Macleod KM, Shepherd M, Ellard S, Hattersley AT. Pregnancy outcome in patients with raised blood glucose due to a heterozygous glucokinase gene mutation. *Diabet Med* 2009; **26**:14–18.

20 Guenat E, Seematter G, Philippe J, Temler E, Jequier E, Tappy L. Counterregulatory responses to hypoglycemia in patients with glucokinase gene mutations. *Diabetes Metab* 2000; **26**:377–384.

21 Spyer G, Hattersley AT, Sykes JE, Sturley RH, MacLeod KM. Influence of maternal and fetal glucokinase mutations in gestational diabetes. *Am J Obstet Gynecol* 2001; **185**:240–241.

22 Velho G, Hattersley AT, Froguel P. Maternal diabetes alters birth weight in glucokinase-deficient (MODY2) kindred but has no influence on adult weight, height, insulin secretion or insulin sensitivity. *Diabetologia* 2000; **43**:1060–1063.

23 Wang H, Maechler P, Hagenfeldt KA, Wollheim CB. Dominant-negative suppression of HNF-1alpha function results in defective insulin gene transcription and impaired metabolism-secretion coupling in a pancreatic beta-cell line. *EMBO J* 1998; **17**:6701–6713.

24 Wang H, Antinozzi PA, Hagenfeldt KA, Maechler P, Wollheim CB. Molecular targets of a human HNF1 alpha mutation responsible for pancreatic beta-cell dysfunction. *EMBO J* 2000; **19**:4257–4264.

25 Shih DQ, Screenan S, Munoz KN, Philipson L, Pontoglio M, Yaniv M, *et al.* Loss of HNF-1alpha function in mice leads to abnormal expression of genes involved in pancreatic islet development and metabolism. *Diabetes* 2001; **50**:2472–2480.

26 Hagenfeldt-Johansson KA, Herrera PL, Wang H, Gjinovci A, Ishihara H, Wollheim CB. Beta-cell-targeted expression of a dominant-negative hepatocyte nuclear factor-1 alpha induces a maturity-onset diabetes of the young (MODY)3-like phenotype in transgenic mice. *Endocrinology* 2001; **142**:5311–5320.

27 Wobser H, Dussmann H, Kogel D, Wang H, Reimertz C, Wollheim CB, *et al.* Dominant-negative suppression of HNF-1 alpha results in mitochondrial dysfunction, INS-1 cell apoptosis, and increased sensitivity to ceramide, but not to high glucose-induced cell death. *J Biol Chem* 2002; **277**:6413–6421.

28 Yamagata K, Nammo T, Moriwaki M, Ihara A, Iizuka K, Yang Q, *et al.* Overexpression of dominant-negative mutant hepatocyte nuclear factor-1 alpha in pancreatic beta-cells causes abnormal islet architecture with decreased expression of E-cadherin, reduced beta-cell proliferation, and diabetes. *Diabetes* 2002; **51**:114–123.

29 Frayling TM, Evans JC, Bulman MP, Pearson E, Allen L, Owen K, *et al.* Beta-cell genes and diabetes: molecular and clinical characterization of mutations in transcription factors. *Diabetes* 2001; **50**(Suppl 1):S94–S100.

30 Shepherd M, Sparkes AC, Hattersley A. Genetic testing in maturity onset diabetes of the young (MODY): a new challenge for the diabetic clinic. *Pract Diabet Int* 2001; **18**:16–21.

31 Harries LW, Ellard S, Stride A, Morgan NG, Hattersley AT. Isomers of the TCF1 gene encoding hepatocyte nuclear factor-1 alpha show differential expression in the pancreas and define the relationship between mutation position and clinical phenotype in monogenic diabetes. *Hum Mol Genet* 2006; **15**:2216–2224.

32 Bellanne-Chantelot C, Carette C, Riveline JP, Valero R, Gautier JF, Larger E, *et al.* The type and the position of HNF1A mutation modulate age at diagnosis of diabetes in patients with maturity-onset diabetes of the young (MODY)-3. *Diabetes* 2008; **57**:503–508.

33 Byrne MM, Sturis J, Menzel S, Yamagata K, Fajans SS, Dronsfield MJ, *et al.* Altered insulin secretory responses to glucose in diabetic and nondiabetic subjects with mutations in the diabetes susceptibility gene MODY3 on chromosome 12. *Diabetes* 1996; **45**:1503–1510.

34 Isomaa B, Henricsson M, Lehto M, Forsblom C, Karanko S, Sarelin L, *et al.* Chronic diabetic complications in patients with MODY3 diabetes. *Diabetologia* 1998; **41**:467–473.

35 Pearson E, McEneny J, Young I, Hattersley A. HDL-cholesterol: differentiating between HNF-1alpha MODY and type 2 diabetes. *Diabet Med* 2003; **20**(Suppl 2):15.

36 Stride A, Ellard S, Clark P, Shakespeare L, Salzmann MB, Shepherd M, *et al.* Beta-cell dysfunction, insulin sensitivity, and glycosuria precede diabetes in hepatocyte nuclear factor-1alpha mutation carriers. *Diabetes Care* 2005; **28**:1751–1756.

37 Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, *et al.* Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med* 2007; **4**:e118.

38 Pearson ER, Pruhova S, Tack CJ, Johansen A, Castleden HA, Lumb PJ, *et al.* Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. *Diabetologia* 2005; **48**:878–885.

39 Ellard S, Bellanne-Chantelot C, Hattersley AT. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. *Diabetologia* 2008; **51**:546–553.

40 Levy-Marchal C, Tichet J, Fajardy I, Gu XF, Dubois F, Czernichow P. Islet cell antibodies in normal French schoolchildren. *Diabetologia* 1992; **35**:577–582.

41 LaGasse JM, Brantley MS, Leech NJ, Rowe RE, Monks S, Palmer JP, *et al.* Successful prospective prediction of type 1 diabetes in schoolchildren through multiple defined autoantibodies: an 8-year follow-up of the Washington State Diabetes Prediction Study. *Diabetes Care* 2002; **25**:505–511.

42 Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* 2003; **362**:1275–1281.

43 Pearson ER, Liddell WG, Shepherd M, Corrall RJ, Hattersley AT. Sensitivity to sulphonylureas in patients with hepatocyte nuclear factor-1alpha gene mutations: evidence for pharmacogenetics in diabetes. *Diabet Med* 2000; **17**:543–545.

44 Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. *Diabet Med* 2009; **26**:437–441.

45 Tuomi T, Honkanen EH, Isomaa B, Sarelin L, Groop LC. Improved prandial glucose control with lower risk of hypoglycemia with nateglinide than with glibenclamide in patients with maturity-onset diabetes of the young type 3. *Diabetes Care* 2006; **29**:189–194.

46 Moretti ME, Rezvani M, Koren G. Safety of glyburide for gestational diabetes: a meta-analysis of pregnancy outcomes. *Ann Pharmacother* 2008; **42**:483–490.

47 Moore TR. Glyburide for the treatment of gestational diabetes: a critical appraisal. *Diabetes Care* 2007; **30**(Suppl 2):S209–S213.

48 Stoffers DA, Stanojevic V, Habener JF. Insulin promoter factor-1 gene mutation linked to early-onset type 2 diabetes mellitus directs expression of a dominant negative isoprotein. *J Clin Invest* 1998; **102**:232–241.

49 Kristinsson SY, Thorolfsdottir ET, Talseth B, Steingrimsson E, Thorsson AV, Helgason T, *et al.* MODY in Iceland is associated with mutations in HNF-1alpha and a novel mutation in NeuroD1. *Diabetologia* 2001; **44**:2098–2103.

50 Liu L, Furuta H, Minami A, Zheng T, Jia W, Nanjo K, *et al.* A novel mutation, Ser159Pro in the NeuroD1/BETA2 gene contributes to the development of diabetes in a Chinese potential MODY family. *Mol Cell Biochem* 2007; **303**:115–120.

51 Malecki MT, Jhala US, Antonellis A, Fields L, Doria A, Orban T, *et al.* Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. *Nat Genet* 1999; **23**:323–328.

52 Plengvidhya N, Kooptiwut S, Songtawee N, Doi A, Furuta H, Nishi M, *et al.* PAX4 mutations in Thais with maturity onset diabetes of the young. *J Clin Endocrinol Metab* 2007; **92**:2821–2826.

53 Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V, Dina C, Hamid YH, Joly E, *et al.* Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. *Proc Natl Acad Sci U S A* 2005; **102**:4807–4812.

54 Iafusco D, Stazi MA, Cotichini R, Cotellessa M, Martinucci ME, Mazzella M, *et al.* Permanent diabetes mellitus in the first year of life. *Diabetologia* 2002; **45**:798–804.

55 Edghill EL, Dix RJ, Flanagan SE, Bingley PJ, Hattersley AT, Ellard S, *et al.* HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. *Diabetes* 2006; **55**:1895–1898.

56 Stoy J, Greeley SA, Paz VP, Ye H, Pastore AN, Skowron KB, *et al.* Diagnosis and treatment of neonatal diabetes: a United States experience. *Pediatr Diabetes* 2008; **9**:450–459.

57 Flanagan SE, Edghill EL, Gloyn AL, Ellard S, Hattersley AT. Mutations in KCNJ11, which encodes Kir6.2, are a common cause of diabetes diagnosed in the first 6 months of life, with the phenotype determined by genotype. *Diabetologia* 2006; **49**:1190–1197.

58 Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. *Endocr Rev* 2008; **29**:265–291.

59 Flanagan SE, Patch AM, Mackay DJ, Edghill EL, Gloyn AL, Robinson D, *et al.* Mutations in ATP-sensitive K^+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. *Diabetes* 2007; **56**:1930–1937.

60 Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, *et al.* Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* 2004; **350**:1838–1849.

61 Proks P, Arnold AL, Bruining J, Girard C, Flanagan SE, Larkin B, *et al.* A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. *Hum Mol Genet* 2006; **15**:1793–1800.

62 Babenko AP, Polak M, Cave H, Busiah K, Czernichow P, Scharfmann R, *et al.* Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N Engl J Med* 2006; **355**:456–466.

63 Ellard S, Flanagan SE, Girard CA, Patch AM, Harries LW, Parrish A, *et al.* Permanent neonatal diabetes caused by dominant, recessive, or compound heterozygous SUR1 mutations with opposite functional effects. *Am J Hum Genet* 2007; **81**:375–382.

64 Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. *Diabetes* 2005; **54**:2503–2513.

65 Pearson ER, Flechtner I, Njolstad PR, Malecki MT, Flanagan SE, Larkin B, *et al.* Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006; **355**:467–477.

66 Stoy J, Edghill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, *et al.* Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc Natl Acad Sci U S A* 2007; **104**:15040–15044.

67 Edghill EL, Flanagan SE, Patch AM, Boustred C, Parrish A, Shields B, *et al.* Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. *Diabetes* 2008; **57**:1034–1042.

68 Proks P, Antcliff JF, Lippiat J, Gloyn AL, Hattersley AT, Ashcroft FM. Molecular basis of Kir6.2 mutations associated with neonatal diabetes or neonatal diabetes plus neurological features. *Proc Natl Acad Sci U S A* 2004; **101**:17539–17544.

69 Koster JC, Cadario F, Peruzzi C, Colombo C, Nichols CG, Barbetti F. The G53D mutation in Kir6.2 (KCNJ11) is associated with neonatal diabetes and motor dysfunction in adulthood that is improved with sulfonylurea therapy. *J Clin Endocrinol Metab* 2008; **93**:1054–1061.

70 Sagen JV, Raeder H, Hathout E, Shehadeh N, Gudmundsson K, Baevre H, *et al.* Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: patient characteristics and initial response to sulfonylurea therapy. *Diabetes* 2004; **53**:2713–2718.

71 Codner E, Flanagan S, Ellard S, Garcia H, Hattersley AT. High-dose glibenclamide can replace insulin therapy despite transitory diarrhea in early-onset diabetes caused by a novel R201L Kir6.2 mutation. *Diabetes Care* 2005; **28**:758–759.

72 Slingerland AS, Hurkx W, Noordam K, Flanagan SE, Jukema JW, Meiners LC, *et al.* Sulphonylurea therapy improves cognition in a patient with the V59M KCNJ11 mutation. *Diabet Med* 2008; **25**:277–281.

73 Mlynarski W, Tarasov AI, Gach A, Girard CA, Pietrzak I, Zubcevic L, *et al.* Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. *Nat Clin Pract Neurol* 2007; **3**:640–645.

74 Edghill EL, Gloyn AL, Goriely A, Harries LW, Flanagan SE, Rankin J, *et al.* Origin of de novo KCNJ11 mutations and risk of neonatal diabetes for subsequent siblings. *J Clin Endocrinol Metab* 2007; **92**:1773–1777.

75 Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. *Diabetes* 2000; **49**:1359–1366.

76 Mackay DJ, Callaway JL, Marks SM, White HE, Acerini CL, Boonen SE, *et al.* Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in ZFP57. *Nat Genet* 2008; **40**:949–951.

77 Gloyn AL, Reimann F, Girard C, Edghill EL, Proks P, Pearson ER, *et al.* Relapsing diabetes can result from moderately activating mutations in KCNJ11. *Hum Mol Genet* 2005; **14**:925–934.

78 Yorifuji T, Nagashima K, Kurokawa K, Kawai M, Oishi M, Akazawa Y, *et al.* The C42R mutation in the Kir6.2 (KCNJ11) gene as a cause of transient neonatal diabetes, childhood diabetes, or later-onset, apparently type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2005; **90**:3174–3178.

79 Colombo C, Delvecchio M, Zecchino C, Faienza MF, Cavallo L, Barbetti F. Transient neonatal diabetes mellitus is associated with a recurrent (R201H) KCNJ11 (KIR6.2) mutation. *Diabetologia* 2005; **48**:2439–2441.

80 de Wet H, Proks P, Lafond M, Aittoniemi J, Sansom MS, Flanagan SE, *et al.* A mutation (R826W) in nucleotide-binding domain 1 of ABCC8 reduces ATPase activity and causes transient neonatal diabetes. *EMBO Rep* 2008; **9**:648–654.

81 Patch AM, Flanagan SE, Boustred C, Hattersley AT, Ellard S. Mutations in the ABCC8 gene encoding the SUR1 subunit of the

KATP channel cause transient neonatal diabetes, permanent neonatal diabetes or permanent diabetes diagnosed outside the neonatal period. *Diabetes Obes Metab* 2007; **9**(Suppl 2):28–39.
82 Temple IK, Shield JP. Transient neonatal diabetes, a disorder of imprinting. *J Med Genet* 2002; **39**:872–875.
83 Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. *Diabet Med* 2008; **25**:383–399.
84 Maassen JA, Janssen GM, 'T Hart LM. Molecular mechanisms of mitochondrial diabetes (MIDD). *Ann Med* 2005; **37**:213–221.
85 Maassen JA, 'T Hart LM, Van Essen E, Heine RJ, Nijpels G, Jahangir Tafrechi RS, *et al.* Mitochondrial diabetes: molecular mechanisms and clinical presentation. *Diabetes* 2004; **53**(Suppl 1):S103–S109.
86 Guillausseau PJ, Massin P, Dubois-LaForgue D, Timsit J, Virally M, Gin H, *et al.* Maternally inherited diabetes and deafness: a multicenter study. *Ann Intern Med* 2001; **134**:721–728.
87 Suzuki S, Hinokio Y, Hirai S, Onoda M, Matsumoto M, Ohtomo M, *et al.* Pancreatic beta-cell secretory defect associated with mitochondrial point mutation of the tRNA(LEU(UUR)) gene: a study in seven families with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS). *Diabetologia* 1994; **37**:818–825.
88 Uimonen S, Moilanen JS, Sorri M, Hassinen IE, Majamaa K. Hearing impairment in patients with 3243A–>G mtDNA mutation: phenotype and rate of progression. *Hum Genet* 2001; **108**:284–289.
89 Remes AM, Majamaa K, Herva R, Hassinen IE. Adult-onset diabetes mellitus and neurosensory hearing loss in maternal relatives of MELAS patients in a family with the tRNA(Leu(UUR)) mutation. *Neurology* 1993; **43**:1015–1020.
90 Guillausseau PJ, Dubois-Laforgue D, Massin P, Laloi-Michelin M, Bellanne-Chantelot C, Gin H, *et al.* Heterogeneity of diabetes phenotype in patients with 3243 bp mutation of mitochondrial DNA (Maternally Inherited Diabetes and Deafness or MIDD). *Diabetes Metab* 2004; **30**:181–186.
91 Oka Y, Katagiri H, Ishihara H, Asano T, Kobayashi T, Kikuchi M. Beta-cell loss and glucose induced signalling defects in diabetes mellitus caused by mitochondrial tRNALeu(UUR) gene mutation. *Diabet Med* 1996; **13**(Suppl 6):S98–S102.
92 Massin P, Dubois-Laforgue D, Meas T, Laloi-Michelin M, Gin H, Bauduceau B, *et al.* Retinal and renal complications in patients with a mutation of mitochondrial DNA at position 3,243 (maternally inherited diabetes and deafness): a case–control study. *Diabetologia* 2008; **51**:1664–1670.
93 Silveiro SP, Canani LH, Maia AL, Butany JW, Gross JL. Myocardial dysfunction in maternally inherited diabetes and deafness. *Diabetes Care* 2003; **26**:1323–1324.
94 Nan DN, Fernandez-Ayala M, Infante J, Matorras P, Gonzalez-Macias J. Progressive cardiomyopathy as manifestation of mitochondrial disease. *Postgrad Med J* 2002; **78**:298–299.
95 Yoshida R, Ishida Y, Hozumi T, Ueno H, Kishimoto M, Kasuga M, *et al.* Congestive heart failure in mitochondrial diabetes mellitus. *Lancet* 1994; **344**:1375.
96 Momiyama Y, Suzuki Y, Ohtomo M, Atsumi Y, Matsuoka K, Ohsuzu F, *et al.* Cardiac autonomic nervous dysfunction in diabetic patients with a mitochondrial DNA mutation: assessment by heart rate variability. *Diabetes Care* 2002; **25**:2308–2313.
97 Majamaa-Voltti K, Peuhkurinen K, Kortelainen ML, Hassinen IE, Majamaa K. Cardiac abnormalities in patients with mitochondrial DNA mutation 3243A>G. *BMC Cardiovasc Disord* 2002; **2**:12.
98 Suzuki Y, Kobayashi T, Taniyama M, Astumi Y, Oka Y, Kadowaki T, *et al.* Islet cell antibody in mitochondrial diabetes. *Diabetes Res Clin Pract* 1997; **35**:163–165.
99 Kobayashi T, Oka Y, Katagiri H, Falorni A, Kasuga A, Takei I, *et al.* Association between HLA and islet cell antibodies in diabetic patients with a mitochondrial DNA mutation at base pair 3243. *Diabetologia* 1996; **39**:1196–1200.
100 Oka Y, Katagiri H, Yazaki Y, Murase T, Kobayashi T. Mitochondrial gene mutation in islet-cell-antibody-positive patients who were initially non-insulin-dependent diabetics. *Lancet* 1993; **342**:527–528.
101 Suzuki S, Hinokio Y, Ohtomo M, Hirai M, Hirai A, Chiba M, *et al.* The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation. *Diabetologia* 1998; **41**:584–588.
102 Donovan LE, Severin NE. Maternally inherited diabetes and deafness in a North American kindred: tips for making the diagnosis and review of unique management issues. *J Clin Endocrinol Metab* 2006; **91**:4737–4742.
103 Edmonds JL, Kirse DJ, Kearns D, Deutsch R, Spruijt L, Naviaux RK. The otolaryngological manifestations of mitochondrial disease and the risk of neurodegeneration with infection. *Arch Otolaryngol Head Neck Surg* 2002; **128**:355–362.
104 Sinnathuray AR, Raut V, Awa A, Magee A, Toner JG. A review of cochlear implantation in mitochondrial sensorineural hearing loss. *Otol Neurotol* 2003; **24**:418–426.
105 Coffinier C, Barra J, Babinet C, Yaniv M. Expression of the vHNF1/HNF1beta homeoprotein gene during mouse organogenesis. *Mech Dev* 1999; **89**:211–213.
106 Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. *J Med Genet* 2006; **43**:84–90.
107 Decramer S, Parant O, Beaufils S, Clauin S, Guillou C, Kessler S, *et al.* Anomalies of the TCF2 gene are the main cause of fetal bilateral hyperechogenic kidneys. *J Am Soc Nephrol* 2007; **18**:923–933.
108 Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1beta. *Nephrol Dial Transplant* 2004; **19**:2703–2708.
109 Ulinski T, Lescure S, Beaufils S, Guigonis V, Decramer S, Morin D, *et al.* Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2) mutations in a pediatric cohort. *J Am Soc Nephrol* 2006; **17**:497–503.
110 Yorifuji T, Kurokawa K, Mamada M, Imai T, Kawai M, Nishi Y, *et al.* Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. *J Clin Endocrinol Metab* 2004; **89**:2905–2908.
111 Bingham C, Ellard S, Allen L, Bulman M, Shepherd M, Frayling T, *et al.* Abnormal nephron development associated with a frameshift mutation in the transcription factor hepatocyte nuclear factor-1 beta. *Kidney Int* 2000; **57**:898–907.
112 Edghill EL, Oram RA, Owens M, Stals KL, Harries LW, Hattersley AT, *et al.* Hepatocyte nuclear factor-1beta gene deletions: a common cause of renal disease. *Nephrol Dial Transplant* 2008; **23**:627–635.
113 Pearson ER, Badman MK, Lockwood CR, Clark PM, Ellard S, Bingham C, *et al.* Contrasting diabetes phenotypes associated with hepatocyte nuclear factor-1alpha and -1beta mutations. *Diabetes Care* 2004; **27**:1102–1107.
114 Bellanne-Chantelot C, Chauveau D, Gautier JF, Dubois-Laforgue D, Clauin S, Beaufils S, *et al.* Clinical spectrum associated with hepato-

cyte nuclear factor-1beta mutations. *Ann Intern Med* 2004; **140**:510–517.

115 Edghill EL, Bingham C, Slingerland AS, Minton JA, Noordam C, Ellard S, *et al.* Hepatocyte nuclear factor-1 beta mutations cause neonatal diabetes and intrauterine growth retardation: support for a critical role of HNF-1beta in human pancreatic development. *Diabet Med* 2006; **23**:1301–1306.

116 Haldorsen IS, Vesterhus M, Raeder H, Jensen DK, Sovik O, Molven A, *et al.* Lack of pancreatic body and tail in HNF1B mutation carriers. *Diabet Med* 2008; **25**:782–787.

117 Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, *et al.* Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet* 1997; **17**:384–385.

118 Lebrun G, Vasiliu V, Bellanne-Chantelot C, Bensman A, Ulinski T, Chretien Y, *et al.* Cystic kidney disease, chromophobe renal cell carcinoma and TCF2 (HNF1 beta) mutations. *Nat Clin Pract Nephrol* 2005; **1**:115–119.

119 Rebouissou S, Vasiliu V, Thomas C, Bellanne-Chantelot C, Bui H, Chretien Y, *et al.* Germline hepatocyte nuclear factor 1alpha and 1beta mutations in renal cell carcinomas. *Hum Mol Genet* 2005; **14**:603–614.

120 Bellanne-Chantelot C, Clauin S, Chauveau D, Collin P, Daumont M, Douillard C, *et al.* Large genomic rearrangements in the hepatocyte nuclear factor-1β (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes* 2005; **54**:3126–3132.

121 d'Annunzio G, Minuto N, D'Amato E, de Toni T, Lombardo F, Pasquali L, *et al.* Wolfram syndrome (diabetes insipidus, diabetes, optic atrophy, and deafness): clinical and genetic study. *Diabetes Care* 2008; **31**:1743–1745.

122 Viswanathan V, Medempudi S, Kadiri M. Wolfram syndrome. *J Assoc Physicians India* 2008; **56**:197–199.

123 Olsen BS, Hahnemann JM, Schwartz M, Ostergaard E. Thiamine-responsive megaloblastic anaemia: a cause of syndromic diabetes in childhood. *Pediatr Diabetes* 2007; **8**:239–241.

124 Iyer S, Korada M, Rainbow L, Kirk J, Brown RM, Shaw N, *et al.* Wolcott–Rallison syndrome: a clinical and genetic study of three children, novel mutation in EIF2AK3 and a review of the literature. *Acta Paediatr* 2004; **93**:1195–1201.

125 Raeder H, Johansson S, Holm PI, Haldorsen IS, Mas E, Sbarra V, *et al.* Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat Genet* 2006; **38**:54–62.

126 Savage DB, Semple RK, Chatterjee VK, Wales JK, Ross RJ, O'Rahilly S. A clinical approach to severe insulin resistance. *Endocr Dev* 2007; **11**:122–132.

127 Ullrich A, Bell JR, Chen EY, Herrera R, Petruzzelli LM, Dull TJ, *et al.* Human insulin receptor and its relationship to the tyrosine kinase family of oncogenes. *Nature* 1985; **313**:756–761.

128 White MF, Kahn CR. The insulin signaling system. *J Biol Chem* 1994; **269**:1–4.

129 Krook A, O'Rahilly S. Mutant insulin receptors in syndromes of insulin resistance. *Baillieres Clin Endocrinol Metab* 1996; **10**:97–122.

130 Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, *et al.* The syndromes of insulin resistance and acanthosis nigricans: insulin-receptor disorders in man. *N Engl J Med* 1976; **294**:739–745.

131 Musso C, Cochran E, Moran SA, Skarulis MC, Oral EA, Taylor S, *et al.* Clinical course of genetic diseases of the insulin receptor (type A and Rabson–Mendenhall syndromes): a 30-year prospective. *Medicine (Baltimore)* 2004; **83**:209–222.

132 Donohue WL, Uchida I. Leprechaunism: a euphemism for a rare familial disorder. *J Pediatr* 1954; **45**:505–519.

133 Kumar S, Tullu MS, Muranjan MN, Kamat JR. Rabson–Mendenhall syndrome. *Indian J Med Sci* 2005; **59**:70–73.

134 Longo N, Wang Y, Pasquali M. Progressive decline in insulin levels in Rabson–Mendenhall syndrome. *J Clin Endocrinol Metab* 1999; **84**:2623–2629.

135 Harris AM, Hall B, Kriss VM, Fowlkes JL, Kiessling SG. Rabson–Mendenhall syndrome: medullary sponge kidney, a new component. *Pediatr Nephrol* 2007; **22**:2141–2144.

136 Semple RK, Soos MA, Luan J, Mitchell S, Wilson JC, Gurnell M, *et al.* Elevated plasma adiponectin in humans with genetically defective insulin receptors. *J Clin Endocrinol Metab* 2006; **91**:3219–3223.

137 Semple RK, Halberg NH, Burling K, Soos MA, Schraw T, Luan J, *et al.* Paradoxical elevation of high-molecular weight adiponectin in acquired extreme insulin resistance due to insulin receptor antibodies. *Diabetes* 2007; **56**:1712–1717.

138 Cochran E, Musso C, Gorden P. The use of U-500 in patients with extreme insulin resistance. *Diabetes Care* 2005; **28**:1240–1244.

139 McDonald A, Williams RM, Regan FM, Semple RK, Dunger DB. IGF-1 treatment of insulin resistance. *Eur J Endocrinol* 2007; **157**(Suppl 1):S51–S56.

140 Garg A. Acquired and inherited lipodystrophies. *N Engl J Med* 2004; **350**:1220–1234.

141 Dunnigan MG, Cochrane MA, Kelly A, Scott JW. Familial lipoatrophic diabetes with dominant transmission: a new syndrome. *Q J Med* 1974; **43**:33–48.

142 Garg A, Peshock RM, Fleckenstein JL. Adipose tissue distribution pattern in patients with familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab* 1999; **84**:170–174.

143 Haque WA, Oral EA, Dietz K, Bowcock AM, Agarwal AK, Garg A. Risk factors for diabetes in familial partial lipodystrophy, Dunnigan variety. *Diabetes Care* 2003; **26**:1350–1355.

144 Garg A. Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab* 2000; **85**:1776–1782.

145 Haque WA, Vuitch F, Garg A. Post-mortem findings in familial partial lipodystrophy, Dunnigan variety. *Diabet Med* 2002; **19**:1022–1025.

146 Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, *et al.* Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* 1999; **402**:880–883.

147 Agarwal AK, Garg A. A novel heterozygous mutation in peroxisome proliferator-activated receptor-gamma gene in a patient with familial partial lipodystrophy. *J Clin Endocrinol Metab* 2002; **87**:408–411.

148 Hegele RA, Cao H, Frankowski C, Mathews ST, Leff T. PPARG F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. *Diabetes* 2002; **51**:3586–3590.

149 Al-Shali K, Cao H, Knoers N, Hermus AR, Tack CJ, Hegele RA. A single-base mutation in the peroxisome proliferator-activated receptor gamma4 promoter associated with altered *in vitro* expression and partial lipodystrophy. *J Clin Endocrinol Metab* 2004; **89**:5655–5660.

150 Agostini M, Schoenmakers E, Mitchell C, Szatmari I, Savage D, Smith A, *et al.* Non-DNA binding, dominant-negative, human

PPARgamma mutations cause lipodystrophic insulin resistance. *Cell Metab* 2006; **4**:303–311.

151 Francis GA, Li G, Casey R, Wang J, Cao H, Leff T, *et al.* Peroxisomal proliferator activated receptor-gamma deficiency in a Canadian kindred with familial partial lipodystrophy type 3 (FPLD3). *BMC Med Genet* 2006; **7**:3.

152 Hegele RA, Ur E, Ransom TP, Cao H. A frameshift mutation in peroxisome-proliferator-activated receptor-gamma in familial partial lipodystrophy subtype 3 (FPLD3; MIM 604367). *Clin Genet* 2006; **70**:360–362.

153 Monajemi H, Zhang L, Li G, Jeninga EH, Cao H, Maas M, *et al.* Familial partial lipodystrophy phenotype resulting from a single-base mutation in deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor-gamma. *J Clin Endocrinol Metab* 2007; **92**:1606–1612.

154 Ludtke A, Buettner J, Wu W, Muchir A, Schroeter A, Zinn-Justin S, *et al.* Peroxisome proliferator-activated receptor-gamma C190S mutation causes partial lipodystrophy. *J Clin Endocrinol Metab* 2007; **92**:2248–2255.

155 Ludtke A, Buettner J, Schmidt HH, Worman HJ. New PPARG mutation leads to lipodystrophy and loss of protein function that is partially restored by a synthetic ligand. *J Med Genet* 2007; **44**:e88.

156 Agarwal AK, Garg A. Genetic basis of lipodystrophies and management of metabolic complications. *Annu Rev Med* 2006; **57**:297–311.

157 Agarwal AK, Simha V, Oral EA, Moran SA, Gorden P, O'Rahilly S, *et al.* Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. *J Clin Endocrinol Metab* 2003; **88**:4840–4847.

158 Chandalia M, Garg A, Vuitch F, Nizzi F. Postmortem findings in congenital generalized lipodystrophy. *J Clin Endocrinol Metab* 1995; **80**:3077–3081.

159 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 1-1975. *N Engl J Med* 1975; **292**:35–41.

160 Van Maldergem L, Magre J, Khallouf TE, Gedde-Dahl T Jr, Delepine M, Trygstad O, *et al.* Genotype–phenotype relationships in Berardinelli–Seip congenital lipodystrophy. *J Med Genet* 2002; **39**:722–733.

161 Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab* 2002; **87**:2395.

162 Kim CA, Delepine M, Boutet E, El Mourabit H, Le Lay S, Meier M, *et al.* Association of a homozygous nonsense caveolin-1 mutation with Berardinelli–Seip congenital lipodystrophy. *J Clin Endocrinol Metab* 2008; **93**:1129–1134.

163 Simha V, Agarwal AK, Aronin PA, Iannaccone ST, Garg A. Novel subtype of congenital generalized lipodystrophy associated with muscular weakness and cervical spine instability. *Am J Med Genet A* 2008; **146A**:2318–2326.

164 Gambineri A, Semple RK, Forlani G, Genghini S, Grassi I, Hyden CS, *et al.* Monogenic polycystic ovary syndrome due to a mutation in the lamin A/C gene is sensitive to thiazolidinediones but not to metformin. *Eur J Endocrinol* 2008; **159**:347–353.

165 Sleilati GG, Leff T, Bonnett JW, Hegele RA. Efficacy and safety of pioglitazone in treatment of a patient with an atypical partial lipodystrophy syndrome. *Endocr Pract* 2007; **13**:656–661.

166 Moreau F, Boullu-Sanchis S, Vigouroux C, Lucescu C, Lascols O, Sapin R, *et al.* Efficacy of pioglitazone in familial partial lipodystrophy of the Dunnigan type: a case report. *Diabetes Metab* 2007; **33**:385–389.

167 Ludtke A, Heck K, Genschel J, Mehnert H, Spuler S, Worman HJ, *et al.* Long-term treatment experience in a subject with Dunnigan-type familial partial lipodystrophy: efficacy of rosiglitazone. *Diabet Med* 2005; **22**:1611–1613.

168 Owen KR, Donohoe M, Ellard S, Hattersley AT. Response to treatment with rosiglitazone in familial partial lipodystrophy due to a mutation in the LMNA gene. *Diabet Med* 2003; **20**:823–827.

169 Savage DB, Tan GD, Acerini CL, Jebb SA, Agostini M, Gurnell M, *et al.* Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-gamma. *Diabetes* 2003; **52**:910–917.

170 Musso C, Javor E, Cochran E, Balow JE, Gorden P. Spectrum of renal diseases associated with extreme forms of insulin resistance. *Clin J Am Soc Nephrol* 2006; **1**:616–622.

171 Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, *et al.* Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002; **346**:570–578.

172 Javor ED, Cochran EK, Musso C, Young JR, Depaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. *Diabetes* 2005; **54**:1994–2002.

173 Musso C, Cochran E, Javor E, Young J, Depaoli AM, Gorden P. The long-term effect of recombinant methionyl human leptin therapy on hyperandrogenism and menstrual function in female and pituitary function in male and female hypoleptinemic lipodystrophic patients. *Metabolism* 2005; **54**:255–263.

174 Guettier JM, Park JY, Cochran EK, Poitou C, Basdevant A, Meier M, *et al.* Leptin therapy for partial lipodystrophy linked to a PPAR-gamma mutation. *Clin Endocrinol* 2008; **68**:547–554.

175 Beltrand J, Beregszaszi M, Chevenne D, Sebag G, De Kerdanet M, Huet F, *et al.* Metabolic correction induced by leptin replacement treatment in young children with Berardinelli–Seip congenital lipoatrophy. *Pediatrics* 2007; **120**:e291–e296.

176 Park JY, Javor ED, Cochran EK, DePaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy. *Metabolism* 2007; **56**:508–516.

177 Ebihara K, Kusakabe T, Hirata M, Masuzaki H, Miyanaga F, Kobayashi N, *et al.* Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. *J Clin Endocrinol Metab* 2007; **92**:532–541.

178 Simha V, Szczepaniak LS, Wagner AJ, DePaoli AM, Garg A. Effect of leptin replacement on intrahepatic and intramyocellular lipid content in patients with generalized lipodystrophy. *Diabetes Care* 2003; **26**:30–35.

179 Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, *et al.* Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J Clin Invest* 2002; **109**:1345–1350.

180 Krentz AJ. Insulin resistance. *Br Med J* 1996; **313**:1385–1389.

181 Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. *Nat Clin Pract Endocrinol Metab* 2008; **4**:200–213.

182 Moller DE, O'Rahilly S. Syndromes of severe insulin resistance. In: Moller DE, ed. *Insulin Resistance*. Chiches.