

## ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

# The diagnosis and management of monogenic diabetes in children and adolescents

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The diagnosis and management of monogenic diabetes in children and adolescents.  
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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at [www.ispad.org](http://www.ispad.org). The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

### Executive summary and Recommendations

- Monogenic diabetes is uncommon, accounting for ~1–4% of pediatric diabetes cases (B).
- All patients diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of monogenic neonatal diabetes mellitus (NDM), as type 1 diabetes is extremely rare in this subgroup (B). In patients diagnosed between 6 and 12 months of age, testing for NDM should be limited to those without islet antibodies as the majority of patients in this age group have type 1 diabetes (B).
- The molecular genetic diagnosis of NDM will give information on which patients have a potassium channel mutation and can be treated with high dose sulfonylureas and which patients have transient

neonatal diabetes mellitus (TNDM), which will resolve but may later relapse. In addition the diagnosis will inform other likely features, e. g., pancreatic exocrine failure and developmental delay (B).

- The diagnosis of maturity-onset diabetes of the young (MODY) should be suspected in cases with:
  - A family history of diabetes in one parent and first degree relatives of that affected parent in patients who lack the characteristics of type 1 diabetes [no islet autoantibodies, low or no insulin requirements 5 yr after diagnosis (stimulated C-peptide >200 pmol/L)] and lack the characteristics type 2 diabetes (marked obesity, acanthosis nigricans).

- Mild stable fasting hyperglycemia which does not progress. Such cases should be tested for glucokinase (*GCK*) gene mutations, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population (B).
- Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (HNF1B-MODY) and macrosomia and/or neonatal hypoglycemia (HNF4A-MODY) (C).
- In familial autosomal dominant symptomatic diabetes, mutations in the hepatocyte nuclear factor 1 $\alpha$  (*HNF1A*) gene (HNF1A-MODY) should be considered as the first diagnostic possibility, while mutations in the *GCK* gene are the most common cause in the absence of symptoms or marked hyperglycemia (B).
- Results of genetic testing should be reported and presented to families in a clear and unambiguous manner, as results may have a major effect on clinical management (E).
- Referral to a specialist in monogenic diabetes or an interested clinical genetics unit is recommended when predictive testing of asymptomatic individuals is requested (E).
- Some forms of MODY diabetes are sensitive to sulfonylureas, such as HNF1A-MODY and HNF4A-MODY (B).
- Mild fasting hyperglycemia due to GCK-MODY is not progressive during childhood; patients do not develop complications (B) and do not respond to low dose insulin or oral agents (C), so should not receive treatment.

## Introduction

Monogenic diabetes results from one or more defects in a single gene. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a *de novo* mutation. Well over 40 different genetic subtypes of monogenic diabetes have been identified to date, each having a typical phenotype and a specific pattern of inheritance.

A familial form of mild diabetes presenting during adolescence or in early adulthood was first described many years ago (1, 2). Even though diabetes presented in young patients, the disease clinically resembled elderly onset non-insulin dependent diabetes and the newly recognized subtype of familial diabetes became known by the acronym MODY (3). As MODY patients passed on the disease to their offspring following an autosomal dominant pattern of inheritance, it was quickly suspected that it might be a monogenic disorder (4). MODY is by far the commonest type of monogenic diabetes. All currently known subtypes of MODY are

caused by dominantly acting heterozygous mutations in genes important for the development or function of  $\beta$  cells (1, 5). Over the last few years, however, a number of forms of monogenic diabetes clinically and genetically different from MODY have been identified (6). Some patients harbor dominant mutations arising *de novo* (i.e., not inherited from parents) so family history suggesting a monogenic condition is lacking (7–9). These facts, along with a widespread lack of awareness, hinder clinical diagnosis so that the majority of children with genetically proven monogenic diabetes are initially misdiagnosed as having type 1 (10–12) or, less commonly, type 2 diabetes (13). Although monogenic diabetes is uncommon, it accounts for 1–4% of pediatric diabetes cases (14–16).

## Clinical relevance of diagnosing monogenic diabetes

Identification of children with monogenic diabetes usually improves their clinical care. Making a specific molecular diagnosis helps predict the expected clinical course of the disease and guide the most appropriate management in a particular patient, including pharmacological treatment. Furthermore, it has important implications for the family as it enables genetic counseling and frequently triggers extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified.

### Selecting candidates for molecular testing

In contrast to type 1 and type 2 diabetes, where there is no single diagnostic test, molecular genetic testing is both sensitive and specific for diagnosing monogenic diabetes. Genetic testing is currently available in many countries around the world and should be strongly considered in patients with suspected monogenic diabetes (see below). Appropriate informed consent/assent must be prospectively obtained from the patient and his/her legal guardians. Genetic testing for some conditions is available free of charge on a research basis in certain academic institutions (e.g., [www.diabetesgenes.org](http://www.diabetesgenes.org), <http://monogenicdiabetes.uchicago.edu>, <http://www.pediatrics.umed.pl/team/en/contact>, [www.mody.no](http://www.mody.no), and <http://www.euro-wabb.org/en/european-genetic-diagnostic-laboratories>).

Next-generation sequencing enables the simultaneous analysis of multiple genes at a lower cost and may become a feasible alternative to traditional genetic testing in the near future (17–20). In the meantime, a judicious approach to selecting candidates for molecular testing is required. The simplest way of maximizing the cost-effectiveness of traditional genetic testing is by

increasing its positive yield through a reasoned selection of the appropriate gene(s) for analysis according to the patient's clinical, immunological, and/or biochemical phenotype (21, 22). This process may be relatively easy to undertake when clinical features directly pointing to a specific syndrome are present, but results may be very difficult to achieve when diabetes is the only manifestation of the monogenic disorder.

When to suspect a diagnosis of type 1 diabetes in children may not be correct?

Features in children initially thought to have type 1 diabetes that suggest a possible diagnosis of monogenic diabetes are shown below. Except for age of diagnosis less than 6 months, none of these are pathognomonic and should be considered together rather than in isolation:

- 1 Diabetes presenting before 6 months of age as type 1 diabetes is extremely rare in this age-group (2, 23).
- 2 Family history of diabetes in one parent and other first degree relatives of that affected parent.
- 3 Absence of islet autoantibodies, especially if measured at diagnosis.
- 4 Preserved  $\beta$ -cell function, with low insulin requirements and detectable C-peptide (either in blood or urine) over an extended partial remission phase (5 yr after diagnosis).

When to suspect a diagnosis of type 2 diabetes in children may not be correct?

In young people, type 2 diabetes often presents around puberty and the majority are obese. A number of features that should suggest monogenic diabetes are listed below:

- 1 Absence of severe obesity.
- 2 Lack of acanthosis nigricans and/or other markers of metabolic syndrome.
- 3 Ethnic background with a low prevalence of type 2 diabetes, e.g., European Caucasian.
- 4 Strong family history of diabetes without obesity.

Interpretation of genetic findings

Despite the obvious clinical benefits derived from an increased awareness and more widely available genetic diagnostic services, care needs to be exercised in the interpretation of genetic findings (24). The way the clinician interprets the genetic report will have a major effect on the further clinical management of the patient and his/her family. Therefore, it is crucial that the results are presented in a clear and unambiguous way

to ensure that both clinicians and patients receive adequate and understandable information. Specific recommendations describing the information that should be included in the molecular genetics laboratory report for MODY testing have been published (25). These include the method used for mutation screening, whether the mutation is novel and if so, evidence for its pathogenicity, and information about the likelihood of the disease being inherited by the offspring. Referral to a specialist unit (diabetes genetics or clinical genetics) is recommended when predictive testing of asymptomatic individuals is requested.

### Specific subtypes of monogenic diabetes and their management

The different forms of monogenic diabetes can be classified according to the main pathogenic mechanism into two separate groups (26): genetic defects of insulin secretion and genetic defects of insulin action. In children, the majority of cases result from mutations in genes causing  $\beta$  cell loss or dysfunction although diabetes can rarely occur from mutations resulting in very severe insulin resistance. From a clinical perspective, clinical scenarios when a diagnosis of monogenic diabetes should be considered include:

- 1 Diabetes presenting before 6 months of age (NDM).
- 2 Autosomal dominant familial mild hyperglycemia or diabetes.
- 3 Diabetes associated with extrapancreatic features.
- 4 Monogenic insulin resistance syndromes.

NDM diabetes diagnosed within the first 6–12 months of life

The clinical presentation of autoimmune type 1 diabetes is exceedingly rare before age 6 months (23, 27). Even though autoantibodies against  $\beta$ -cell antigens may be occasionally found in very young diabetic infants (23), it is now accepted that *FOXP3* mutations, and not type 1 diabetes, will account for most of these cases (28). Therefore, all patients diagnosed under 6 months should have genetic testing for monogenic NDM. Some cases of monogenic diabetes can be diagnosed between 6 and 12 months (12, 29, 30) although the vast majority of these patients have type 1 diabetes.

Many patients with NDM are born small for gestational age, which reflects a prenatal deficiency of insulin secretion as insulin exerts potent growth-promoting effects during intrauterine development (31). Approximately half will require lifelong treatment to control hyperglycemia - permanent neonatal diabetes mellitus (PNDM). In the remaining cases, diabetes will remit within a few weeks or months

- transient neonatal diabetes mellitus (TNDM), although it might relapse later in life. In both situations, diabetes presents more frequently as an isolated condition, but some patients show a variety of associated extra-pancreatic clinical features pointing to a particular gene, which may help guide genetic testing (Table 1).

The genetic basis of TNDM has been mostly uncovered: approximately two thirds of cases are caused by abnormalities in an imprinted region on chromosome 6q24 (32, 33), with activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium ( $K_{ATP}$ ) channel of the  $\beta$ -cell membrane (*KCNJ11* or *ABCC8*) causing the majority of the remaining cases (34). A minority of cases of TNDM is caused by mutations in other genes, including *HNF1B* (35), *INS* (preproinsulin gene) (36), etc. In contrast, the genetic abnormality responsible for up to 30% of PNDM cases remains unknown, although the commonest known cause in outbred populations are mutations in the  $K_{ATP}$  channel or *INS* genes (37, 38). If parents are related, Wolcott–Rallison syndrome or homozygous mutations in the *GCK* gene are the most common etiologies (37).

#### Transient neonatal diabetes from imprinting anomalies on 6q24

Anomalies at the 6q24 locus, spanning two candidate genes *PLAGL1* and *HYMAI*, are the single most common cause of neonatal diabetes and always result in TNDM (39). In normal circumstances, this region is maternally imprinted so that only the allele inherited from the father is expressed. TNDM is ultimately associated with overexpression of the imprinted genes (40), with three different molecular mechanisms identified to date: paternal uniparental disomy of chromosome 6 (either complete or partial; it accounts for 50% of sporadic TNDM cases), unbalanced paternal duplication of 6q24 (found in most familial cases), and abnormal methylation of the maternal allele (found in some sporadic cases) (41). Methylation defects may affect only the 6q24 locus or may arise in the context of a generalized hypomethylation syndrome along with other clinical features including congenital heart defects, brain malformations, etc. (42). Some cases of TNDM secondary to multiple methylation defects are caused by recessively acting mutations in *ZFP57*, a gene on chromosome 6p involved in the regulation of DNA methylation (43).

Patients with 6q24 abnormalities are born with severe intrauterine growth retardation and develop severe but non-ketotic hyperglycemia very early on, usually during the first week of life (41, 44). Despite the severity of the initial presentation, the insulin dose can be tapered quickly so that the majority of patients do

not require any treatment by a median age of 12 wk. One third of patients show macroglossia and, more rarely, an umbilical hernia is present. During remission, transient hyperglycemia may occur during intercurrent illnesses (45). Over time, diabetes relapses in at least 50–60% of patients, usually around puberty, although recurrences have been reported as young as 4 yr of age. Relapse clinically resembles early-onset type 2 diabetes and is characterized by a loss of the first-phase insulin secretion. Insulin therapy is not always necessary (there is usually some response to oral sulfonylureas) and, if needed, insulin doses required tend to be lower than in patients with type 1 diabetes.

The phases described above do not present irretrievably in every patient. Interestingly, some mutation carrier relatives develop type 2 diabetes or gestational diabetes in adulthood without any evidences of having had neonatal diabetes, suggesting that other genetic or epigenetic factors may influence the clinical expression alterations of chromosome 6q24 (32).

The role of genetic counseling depends on the underlying molecular mechanism. Uniparental disomy of chromosome 6 is generally sporadic and therefore the risk of recurrence in siblings and offspring is low. When paternal duplication of the 6q24 region is found, males have a 50% chance of transmitting the mutation and the disease to their children. In contrast, females will pass on the duplication but their children will not develop the disease. In this case, TNDM may recur in the next generation as their asymptomatic sons pass on the molecular defect to their own children. Some methylation defects (i.e., *ZFP57* mutations) show an autosomal recessive inheritance and hence the recurrence risk is 25% for siblings and almost negligible for the offspring of a patient.

#### Neonatal diabetes due to mutations in the $K_{ATP}$ channel genes

$K_{ATP}$  channels are hetero-octameric complexes formed by four pore-forming Kir6.2 subunits and four SUR1 regulatory subunits, encoded by the genes *KCNJ11* and *ABCC8*, respectively (46). They regulate insulin secretion by linking intracellular metabolic state to the  $\beta$ -cell membrane electrical activity. Any increase in the intracellular metabolic activity induces an increase in the ATP/ADP ratio within the pancreatic  $\beta$ -cell which makes the  $K_{ATP}$  channels close, and leads to the cell membrane depolarization which ultimately triggers insulin secretion (47). Activating mutations in *KCNJ11* or *ABCC8*, which prevent  $K_{ATP}$  channel closure and hence insulin secretion in response to hyperglycemia, are the most common cause of PNDM (7, 48–51) and the second most common cause of TNDM (34).

The majority of patients with mutations in *KCNJ11* have PNDM rather than TNDM (90 vs. 10%). In

Table 1. Monogenic subtypes of neonatal and infancy-onset diabetes (modified from reference 37)

Gene	Locus	Inheritance	Other clinical features	References
Abnormal pancreatic development				
<i>PLAGL1/HYMAI</i>	6q24	Variable (imprinting)	TNDM ± macroglossia ± umbilical hernia	(33)
<i>ZFP57</i>	6p22.1	Recessive	TNDM (multiple hypomethylation syndrome) ± macroglossia ± developmental delay ± umbilical defects ± congenital heart disease	(43)
<i>PDX1</i>	13q12.1	Recessive	PNDM + pancreatic agenesis (steatorrhea)	(173)
<i>PTF1A</i>	10p12.2	Recessive	PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction	(174)
<i>PTF1A</i> enhancer	10p12.2	Recessive	PNDM + pancreatic agenesis without CNS features	(89)
<i>HNF1B</i>	17q21.3	Dominant	TNDM + pancreatic hypoplasia and renal cysts	(35)
<i>RFX6</i>	6q22.1	Recessive	PNDM + intestinal atresia + gall bladder agenesis	(175)
<i>GATA6</i>	18q11.1-q11.2	Dominant	PNDM + pancreatic agenesis + congenital heart defects + biliary abnormalities	(90)
<i>GATA4</i>	8p23.1	Dominant	PNDM + pancreatic agenesis + congenital heart defects	(176)
<i>GLIS3</i>	9p24.3-p23	Recessive	PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts	(177)
<i>NEUROG3</i>	10q21.3	Recessive	PNDM + enteric anendocrinosis (malabsorptive diarrhea)	(178)
<i>NEUROD1</i>	2q32	Recessive	PNDM + cerebellar hypoplasia + visual impairment + deafness	(179)
<i>PAX6</i>	11p13	Recessive	PNDM + microphthalmia + brain malformations	(180)
<i>MXN1</i>	7q36.3	Recessive	PNDM + developmental delay + sacral agenesis + imperforate anus	(181) (175)
<i>NKX2-2</i>	20p11.22	Recessive	PNDM + developmental delay + hypotonia + short stature + deafness + constipation	(182)
Abnormal β-cell function				
<i>KCNJ11</i>	11p15.1	Spontaneous or dominant	PNDM/TNDM ± DEND	(7)
<i>ABCC8</i>	11p15.1	Spontaneous, dominant or recessive	TNDM/PNDM ± DEND	(48)
<i>INS</i>	11p15.5	Recessive	Isolated PNDM or TNDM	(36)
<i>GCK</i>	7p15-p13	Recessive	Isolated PNDM	(83)
<i>SLC2A2 (GLUT2)</i>	3q26.1-q26.3	Recessive	Fanconi–Bickel syndrome: PNDM + hypergalactosemia, liver dysfunction	(183)
<i>SLC19A2</i>	1q23.3	Recessive	Roger’s syndrome: PNDM + thiamine-responsive megaloblastic anemia, sensorineural deafness	(184)
Destruction of β cells				
<i>INS</i>	11p15.5	Spontaneous or dominant	Isolated PNDM	(9)
<i>EIF2AK3</i>	2p11.2	Recessive	Wolcott–Rallison syndrome: PNDM + skeletal dysplasia + recurrent liver dysfunction	(77)
<i>IER3IP1</i>	18q21.2	Recessive	PNDM + microcephaly + lissencephaly + epileptic encephalopathy	(185)
<i>FOXP3</i>	Xp11.23-p13.3	X-linked, recessive	IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, and elevated IgE)	(186)
<i>WFS1</i>	4p16.1	Recessive	PNDM* + optic atrophy ± diabetes insipidus ± deafness	(126)

CNS, central nervous system; DEND, developmental delay, epilepsy, and neonatal diabetes syndrome; IgE, immunoglobulin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; TNDM; transient neonatal diabetes mellitus.

\*The mean age of diagnosis among patients with *WFS1* mutations is approximately 5 yr (129).

contrast, mutations in *ABCC8* cause TNDM more frequently (~66%) (48, 52). There are no significant differences between the two subtypes of neonatal diabetes regarding the severity of intrauterine growth retardation or the age at diagnosis of diabetes (34, 53). Patients with  $K_{ATP}$  channel mutations typically show milder intrauterine growth retardation and are diagnosed slightly later than patients with 6q24 abnormalities, indicating a less severe insulin deficiency during the last months of intrauterine development and at the time birth. In  $K_{ATP}$ -TNDM patients, diabetes usually remits later and relapses earlier than in 6q24-TNDM (34).

Presenting clinical features in patients with  $K_{ATP}$  channel activating mutations suggest insulin dependency, with low or undetectable C-peptide levels and frequent presentation with diabetic ketoacidosis (54). In addition to diabetes, about 20% of patients with mutations in *KCNJ11* were initially found to present with associated neurological features (7, 54, 55) in keeping with the expression of  $K_{ATP}$  channels in neurons and muscle cells (47, 56). The most severe defect included marked developmental delay and early-onset epilepsy and became known as DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome. An intermediate DEND syndrome characterized by neonatal diabetes and less severe developmental delay without epilepsy is more common. Neurological features were considered less frequent and usually milder in patients with mutations in *ABCC8* (48, 49). However, a recent study suggested that mild neurodevelopmental abnormalities, including developmental coordination disorder (particularly visual-spatial dyspraxia) or attention deficits, might be found on detailed testing in all patients with  $K_{ATP}$  channel mutations (57).

Approximately 90% of patients with activating mutations in the  $K_{ATP}$  channel genes can be transferred from insulin onto sulfonylurea tablets (58, 59). Transfer usually improves glycemic control without increasing the risk of hypoglycemia. The doses required are high when calculated on a per kg body weight basis compared with adults with type 2 diabetes, typically needing around 0.5 mg/kg/d of glibenclamide, although doses as high as 2.3 mg/kg/d have been occasionally reported (60, 61). Many patients have been able to progressively reduce the dose of sulfonylurea after transition while maintaining excellent glycemic control (58, 62). The only side effects reported to date are transient diarrhea and staining of the teeth (63, 64). Some brain imaging studies have shown that sulfonylurea drugs may penetrate blood–brain barrier (65, 66) and very interesting case reports suggest that sulfonylureas may partially improve some of the neurological symptoms (67–70).

Activating mutations in *KCNJ11* causing neonatal diabetes are always heterozygous. As about 90% of

these mutations arise *de novo*, there is usually no family history of neonatal diabetes (71) but familial cases show an autosomal dominant inheritance. Recurrence risk for the offspring of an affected patient is 50%. This is also true for most patients with activating mutations in *ABCC8*. However, some patients are homozygous or compound heterozygous for two different mutations and neonatal diabetes is recessively inherited (49). In this case, the risk of neonatal diabetes for future siblings is 25% but almost inexistent for the offspring. Germline mosaicism (mutations present in the gonads but not detectable in blood) has been reported in several families (71) and hence unaffected parents of a child with an apparently *de novo* mutation should be advised that the recurrence risk in siblings is low but not negligible.

#### Neonatal diabetes due to mutations in *INS* gene

Heterozygous coding mutations in the *INS* gene are the second most common cause of PNDM after  $K_{ATP}$  channel mutations (9, 53, 72, 73). The mutation usually results in a misfolded proinsulin molecule that is trapped and accumulated in the endoplasmic reticulum, leading to endoplasmic reticulum stress and  $\beta$ -cell apoptosis (74).

The severity of intrauterine growth retardation in patients with heterozygous *INS* mutations is similar to that of patients with  $K_{ATP}$  channel mutations. In contrast, diabetes presents at a slightly later age although the ranges overlap greatly and patients do not present with neurological features as a direct consequence of the mutation (53).

The majority of heterozygous *INS* mutations are sporadic *de novo* mutations. Only about 20% of probands have a positive family history of autosomal dominant neonatal diabetes (53). Occasionally, *INS* mutations cause permanent diabetes after 6 months of age and therefore genetic testing should be considered in certain situations, especially in patients with antibody-negative type 1 diabetes (12, 73, 75, 76).

In addition to heterozygous *INS* mutations, homozygous or compound heterozygous mutations causing neonatal diabetes have also been described (36). Biallelic mutations do not cause slowly progressive  $\beta$ -cell destruction but result in a lack of insulin biosynthesis before and after birth, which explains much lower birth weights and earlier presentation of diabetes in affected children. As the disease is recessively inherited, there is a 25% recurrence risk in siblings but, in the absence of consanguinity, a very low risk for the offspring of a patient.

#### Wolcott–Rallison syndrome

Biallelic mutations in *EIF2AK3* (eukaryotic translation initiation factor alpha 2-kinase 3) cause a rare

autosomal recessive syndrome characterized by early-onset diabetes mellitus, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction (77, 78). *EIF2AK3* encodes a protein involved in the regulation of the endoplasmic reticulum stress response. Pancreatic development is rather normal in the absence of the functional protein but misfolded proteins accumulate within the endoplasmic reticulum after birth and eventually induce  $\beta$ -cell apoptosis. Although diabetes usually manifests during infancy, it might not present until 3–4 yr of age. Diabetes may be the first clinical manifestation of the syndrome and therefore this diagnosis needs to be considered in children with PNDM especially if parental consanguinity is present or the patient originates from a highly inbred population (79, 80). As the disease is recessively inherited, there is a 25% recurrence risk in siblings but in the absence of consanguinity, a very low risk for the offspring of a patient.

### Neonatal diabetes due to *GCK* mutations

The enzyme glucokinase is considered the glucose sensor of the  $\beta$  cells, as it catalyzes the rate-limiting step of glucose phosphorylation and therefore enables the  $\beta$  cell to respond appropriately to the degree of glycemia (81). Heterozygous mutations in the *GCK* gene produce familial mild non-progressive hyperglycemia (see below). However, complete glucokinase deficiency secondary to mutations in both alleles, either homozygous or compound heterozygous, prevents the  $\beta$  cells from secreting insulin in response to hyperglycemia (82, 83). For this reason, patients present with severe intrauterine growth retardation, are usually diagnosed with diabetes during the first few days of life, and require exogenous insulin therapy. Apart from diabetes, patients do not show any relevant extrapancreatic features.

*GCK* is responsible for not more than 2–3% of cases of PNDM overall (37). This type of PNDM is inherited in a recessive manner so the recurrence risk for future siblings is 25%. This diagnosis should be strongly considered in probands born to parents with asymptomatic mild hyperglycemia and therefore measuring fasting blood glucose in the parents of any child with neonatal diabetes, even when there is no known consanguinity or family history of diabetes, is often recommended. Sulfonylurea treatment has been tested with no clear effect (P. R. N. and A. T. H., unpublished observations).

### IPEX syndrome

Mutations in the *FOXP3* gene are responsible for the IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome (84, 85). This is the only well-established form of PNDM that is associated

with  $\beta$ -cell autoimmunity and pancreatic islet autoantibodies. Among male infants who present with diabetes, immune deficiency, and/or life-threatening infection, mutations in *FOXP3* should be considered. Treatment with immunosuppressive agents (sirolimus or steroids) is recommended (86, 87). Alternatively, allogeneic bone marrow transplantation with reduced-intensity conditioning should be considered (88).

### Other causes of neonatal diabetes

The clinical features in other causes of neonatal and infancy-onset diabetes are shown in Table 1. Pancreatic scanning is unreliable in neonates and so it is best to use functional tests of exocrine pancreatic function (fecal elastase and fecal fats) when assessing if pancreatic aplasia is present (89, 90). Apart from  $K_{ATP}$  channel neonatal diabetes, all other causes need to be treated with subcutaneous insulin. Patients with pancreatic aplasia/hypoplasia will also require exocrine pancreatic supplements.

Genetic testing should be performed as soon as diabetes is diagnosed in a child aged less than 6 months

Genetic testing will allow diagnosis of a specific type of monogenic diabetes in over 80% of patients whose diabetes is diagnosed before the age of 6 months. As discussed above, this will influence treatment as well as prediction of clinical features. This means that molecular genetic testing is now recommended at the time of diabetes diagnosis in child aged less than 6 months. It is no longer necessary to wait to see if the diabetes resolves or for other features to develop, as major labs will offer comprehensive testing of all NDM subtypes as well as very rapid testing of subtypes that alter treatment.

### Autosomal dominant familial mild hyperglycemia or diabetes (MODY)

The different genetic subtypes of MODY differ in age of onset, pattern of hyperglycemia, and response to treatment. Most of them cause isolated diabetes and therefore may be misdiagnosed as either familial type 1 or type 2 diabetes (10, 13, 91). Although the classic criteria for MODY include family history of diabetes, sporadic *de novo* mutations in a number of causative genes have been reported (92).

Three genes are responsible for the majority of MODY cases (*GCK*, *HNF1A*, and *HNF4A*) and will be described in some detail below (see also Table 2). However, up to 13 different genes have been reported to cause autosomal dominant non-insulin dependent diabetes but these are so unusual they do not need to be

Table 2. Common subtypes of MODY and associated clinical features

Gene	Locus	Clinical features	Treatment	References
<i>HNF4A</i>	20q12-q13.1	Macrosomia and neonatal hypoglycemia, renal Fanconi syndrome (mutation specific)	Sulfonylurea	(187)
<i>GCK</i>	7p15-p13	Mild asymptomatic hyperglycemia	Nil/diet	(188)
<i>HNF1A</i>	12q24.2	Renal glucosuria	Sulfonylurea	(189)
<i>HNF1B</i>	17q12	Renal developmental abnormalities, genital tract malformations	Insulin	(190)

MODY, maturity-onset diabetes of the young.

tested for in children with diabetes except in a research setting or when there are additional phenotypes such as pancreatic exocrine dysfunction (93).

Mild fasting hyperglycemia due to glucokinase gene mutations (*GCK*-MODY, MODY2)

The incidental finding of mild hyperglycemia (5.5–8 mmol/L or 100–145 mg/dL) in otherwise asymptomatic children and adolescents raises the possibility that these patients subsequently develop type 1 or type 2 diabetes. In the absence of concomitant pancreatic autoimmunity, the risk of future type 1 diabetes is minimal (94) and a significant proportion will have a heterozygous mutation in *GCK* (95, 96). In peripubertal children and adolescents, the lack of obesity or other signs of insulin resistance should raise concern about a diagnosis of type 2 diabetes.

*GCK*-MODY is the commonest subtype of monogenic diabetes in the pediatric diabetes clinic and its clinical phenotype is remarkably homogeneous among patients. In contrast to other subtypes of monogenic diabetes, *GCK*-MODY patients regulate insulin secretion adequately but around a slightly higher set point than normal subjects. As a result, they show non-progressive mild hyperglycemia from birth (97). Their hemoglobin A1c (HbA1c) is mildly elevated but usually below 7.5% (98). Despite the mild fasting hyperglycemia, there is usually a small increment in blood glucose during an oral glucose tolerance test (<60 mg/dL or <3.5 mmol/L) (99), although this should not be considered an absolute criterion because of the variability of the oral glucose tolerance test (OGTT). As the degree of hyperglycemia is not high enough to cause osmotic symptoms, most cases are usually diagnosed incidentally when blood glucose is measured for any other reason. Very often, the affected parent remains undiagnosed or has been misdiagnosed with early-onset type 2 diabetes. Measuring fasting glucose in apparently unaffected parents is important when considering a diagnosis of a glucokinase mutation.

As blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely

associated with chronic microvascular or macrovascular complications of diabetes (100, 101) and patients do not generally require any treatment (102). Of note, the presence of a *GCK* mutation does not protect against the concurrent development of polygenic type 2 diabetes later in life, which occurs at a similar prevalence than in the general population (103). *GCK*-PNDM may manifest in *GCK*-MODY families since in the setting of consanguinity or a second *de novo* mutation.

Familial diabetes due to *HNF1A*-MODY (MODY3) and *HNF4A*-MODY (MODY1)

The possibility of monogenic diabetes should be considered whenever a parent of a diabetic child has diabetes, even if they are thought to have type 1 or type 2 diabetes. *HNF1A*-MODY is the most common form of monogenic diabetes that results in familial symptomatic diabetes, with heterozygous *HNF1A* mutations being about 10 times more frequent than heterozygous mutations in *HNF4A* (104). Therefore, *HNF1A*-MODY is the first diagnostic possibility to be considered in families with autosomal dominant symptomatic diabetes.

In both *HNF1A*-MODY and *HNF4A*-MODY, glucose intolerance usually becomes evident during adolescence or early adulthood. In the early stages of the disease, fasting blood glucose may be normal but patients tend to show a large increment in blood glucose (>80 mg/dL or 5 mmol/L) after meals or at 2 h during an OGTT (99). Patients with *HNF1A*-MODY demonstrate impaired incretin effect and inappropriate glucagon responses to OGTT (105). Over time, fasting hyperglycemia and osmotic symptoms (polyuria and polydipsia) present but patients rarely develop ketosis because some residual insulin secretion persists for many years. Chronic complications of diabetes are frequent and their development is related to the degree of metabolic control (106). The frequency of microvascular complications (retinopathy, nephropathy, and neuropathy) is similar to that of patients with type 1 and type 2 diabetes. *HNF1A* mutations are associated with an increased frequency of cardiovascular disease (107).



Mutations in *HNF1A* show a high penetrance so that 63% of mutation carriers develop diabetes before 25 yr of age, 79% before age 35 and 96% before 55 yr (6). The age at diagnosis of diabetes is partly determined by the location of the mutation within the gene (108, 109). Patients with mutations affecting the terminal exons (8–10) are diagnosed, on average, 8 yr later than those with mutations in exons 1–6. On the other hand, exposure to maternal diabetes *in utero* (when the mutation is maternally inherited) brings forward the age at onset of diabetes by about 12 yr (99). In the pediatric population, diabetes in *HNF4A* mutation carriers tend to appear at a similar age to patients with mutations in *HNF1A* (16).

There are some differential clinical characteristics between patients with mutations in *HNF4A* and *HNF1A* that can help decide which gene should be considered first in a particular family.

- Patients with *HNF1A* mutations typically have a low renal threshold for glucose reabsorption due to impaired renal tubular transport of glucose and may present postprandial glycosuria before developing significant hyperglycemia (110).
- In addition to diabetes, carriers of the R76W mutation in *HNF4A* present with an atypical form of Fanconi syndrome including hypercalciuria and nephrocalcinosis (111).
- About 50% of *HNF4A* mutation carriers are macrosomic at birth and 15% have diazoxide-responsive neonatal hyperinsulinemic hypoglycemia (112). In this case, hyperinsulinism typically remits during infancy and patients develop diabetes from adolescence (113, 114). Recently, hyperinsulinemic hypoglycemia has also been reported in *HNF1A* mutation carriers (115) but this is very uncommon.

Patients with both *HNF1A*- and *HNF4A*-MODY can initially be treated with diet although they will have marked postprandial hyperglycemia with high carbohydrate food (99). Most patients will need pharmacological treatment as they show progressive deterioration in glycemic control. They are extremely sensitive to sulfonylureas (116), which usually allow a better glycemic control than that achieved on insulin, especially in children and young adults (117). The initial dose should be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia. As long as the patients do not have problems with hypoglycemia, they can be maintained on low-dose sulfonylureas (e.g., 20–40 mg gliclazide daily) for decades (118, 119). If there is hypoglycemia despite dose titration of a once or twice daily sulfonylurea preparation, a slow release preparation or meal time doses with a short-acting agent such as nateglinide may be considered (120, 121). A recent randomized controlled trial

comparing a glucagon-like peptide (GLP-1) agonist with a sulfonylurea demonstrated lower fasting glucose in those treated with the GLP-1 agonist (122).

### Genetic syndromes associated with diabetes

A monogenic disorder should be considered in any child with diabetes associated with multi-system extrapancreatic features (123). These syndromes may either cause neonatal diabetes (Table 1) or present later in life (see below). The online Mendelian inheritance in Man website ([www.ncbi.nlm.nih.gov/omim](http://www.ncbi.nlm.nih.gov/omim) or [www.omim.org](http://www.omim.org)) can help with clinical features and to know if the gene for a particular syndrome has been defined and hence molecular genetic testing is available. Genetic testing for some of these conditions is available on a research basis at [www.euro-wabb.org](http://www.euro-wabb.org) (124). The most common syndromes usually presenting beyond infancy are described in some detail below.

Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness syndrome (Wolfram syndrome)

The association of diabetes with progressive optic atrophy below 16 yr of age is diagnostic of this autosomal recessive syndrome (125). Non-autoimmune insulin-deficient diabetes is usually the first manifestation of the disease and presents at a mean age of 6 yr, although may present anytime from early-infancy (126, 127). Patients require insulin treatment from diagnosis. Other typical clinical features, such as sensorineural deafness, central diabetes insipidus, urinary tract dilatations, and neurological symptoms develop later in a variable order even within the same family. Many patients with Wolfram Syndrome (WFS) are initially diagnosed as having type 1 diabetes; subsequent loss of vision, which occurs approximately 4 yr after diabetes diagnosis, may be misdiagnosed as diabetic retinopathy (128, 129). Patients WFS die at a median age of 30 yr, mainly from neurodegenerative complications.

At least 90% of patients harbor recessively acting mutations in the *WFS1* gene (130, 131). A second variant of the syndrome has recently been described in association with mutations in *CISD2* (132). Patients with this rare variant do not develop diabetes insipidus but present with additional symptoms including bleeding diathesis and peptic ulcer disease.

Renal cysts and diabetes syndrome (*HNF1B*-MODY or MODY5)

Although initially described as a rare subtype of familial diabetes, it is now clear that patients with heterozygous mutations in *HNF1B* rarely present with isolated diabetes (133). In contrast, renal developmental disorders (especially renal cysts and renal dysplasia) are present in almost all patients

with *HNF1B* mutations or gene deletions (8) and constitute the main presentation in children, even in the absence of diabetes (134). Genital-tract malformations (particularly uterine abnormalities), hyperuricemia and gout can also occur, as well as abnormal liver function tests (133). Diabetes develops later, typically during adolescence or early adulthood (135, 136), although transient neonatal diabetes has been reported in a few cases (35, 137). In addition to insulin deficiency related to pancreatic hypoplasia (138), patients also show some degree of hepatic insulin resistance (139), which explains why they do not respond adequately to sulfonylurea treatment and require early insulin therapy (6). Moreover, mutation carriers have lower exocrine pancreatic function with reduced fecal elastase; this involves both ductal and acinar cells (140). Therefore, the phenotype of renal cysts and diabetes (RCAD) patients is highly variable even within families sharing the same *HNF1B* mutation and therefore this diagnosis should be considered not only in the diabetes clinic but also in other clinics (nephrology, urology, gynecology, etc.). In patients found to have renal cysts, imaging of the pancreas is indicated, as the absence of the pancreatic body and/or tail is highly indicative of *HNF1B*-MODY (141). Fecal elastase should also be measured, as this is always abnormal in patients with *HNF1B*-MODY (140). Importantly, a family history of renal disease or diabetes is not essential to prompt genetic testing, as spontaneous mutations and deletions of this gene are common (one third to two thirds of cases) (8, 134).

#### Mitochondrial diabetes

Diabetes due to mitochondrial mutations and deletions is rarely seen in the pediatric age group as the vast majority of patients develop diabetes as young or middle-aged adults. The most common form of mitochondrial diabetes is caused by the m.3243A>G mutation in mitochondrial DNA. Diabetes onset is usually insidious but approximately 20% of patients have an acute presentation, even in diabetic ketoacidosis (142). Although it typically presents in adulthood, some cases have been reported in adolescents with a high degree of heteroplasmy (143, 144). Mitochondrial diabetes should be suspected in patients presenting with diabetes and sensorineural hearing loss inherited from mother's side. Interestingly, the same m.3243A>G mutation also causes a much more severe clinical syndrome known as MELAS (myopathy, encephalopathy, lactic acidosis, and stroke) (145).

Patients with mitochondrial diabetes may respond initially to diet or oral hypoglycemic agents but often require insulin treatment within months or years. Metformin should be avoided as it interferes with

mitochondrial function and may trigger episodes of lactic acidosis (146).

The penetrance of diabetes in mutation carriers depends on the age considered, but is estimated to be above 85% at 70 yr (142). Affected males do not transmit the disease to their offspring. In contrast, females transmit the mutation to all their children, although some may not develop the disease (6). In addition to the m.3243A>G mutation, early-onset diabetes (even in infancy) has been reported in other less common mitochondrial disorders such as Kearns–Sayre syndrome (147) and Pearson syndrome (148).

#### Diabetes secondary to monogenic diseases of the exocrine pancreas

Heterozygous mutations in *CEL*, which encodes a pancreatic lipase, cause an autosomal dominant disorder of pancreatic exocrine insufficiency and diabetes (93). Importantly, the exocrine component of the syndrome is initiated already in childhood, 10–30 yr before diabetes develops, and can be revealed by lowered fecal elastase and/or pancreatic lipomatosis (149, 150). Other autosomal dominant monogenic diseases affecting mainly the exocrine pancreas that can lead to diabetes sooner or later include cystic fibrosis (*CFTR*) (151), hereditary pancreatitis (*PRSSI* and *SPINK1*) (152), and pancreatic agenesis/hypoplasia (*GATA6*) (90).

#### Monogenic insulin resistance syndromes

The key features of insulin resistance syndromes are moderate to severe acanthosis nigricans associated with either severely increased insulin concentrations or increased insulin requirements (depending on whether the patient has diabetes already), usually in the absence of a corresponding degree of obesity. Three different groups have been proposed based on the pathogenesis of the disease: primary insulin signaling defects, insulin resistance secondary to adipose tissue abnormalities, and insulin resistance as a feature of complex syndromes (153). Clinical and biochemical characterization of patients with severe insulin resistance may be used to guide genetic testing, as it happens with monogenic  $\beta$ -cell diabetes (Table 3). However, diabetes associated with monogenic severe insulin resistance is far less common than monogenic  $\beta$ -cell failure, especially in prepubertal children as hyperglycemia is usually a late event in the natural history of these disorders (154). As ovarian hyperandrogenism usually is the commonest presentation in adolescents, there is a gender bias in the diagnosis. The most relevant disorders are briefly described below.

Table 3. Classification of syndromes of severe insulin resistance (modified from reference 154)

Insulin resistance syndrome subtype		Gene (inheritance)	Leptin	Adiponectin	Other clinical features
Primary insulin signaling defects Adipose tissue abnormalities	Receptor defect	<i>INSR</i> (AR or AD)	Decreased	Normal or elevated	No dyslipidemia No fatty liver
	Post receptor defects	<i>AKT2</i> , <i>TBC1D4</i> (AD)	Increased (low in <i>LEP</i> )		Tall stature ( <i>MC4R</i> ) Hypogonadism ( <i>LEP</i> ) Hypoadrenalism ( <i>POMC</i> )
	Monogenic obesity	<i>MC4R</i> (AD) <i>LEP</i> , <i>LEPR</i> , <i>POMC</i> (AR) Others			Severe dyslipidemia (high triglycerides, low HDL cholesterol) Fatty liver
Congenital generalized lipodystrophy	<i>AGPAT2</i> , <i>BSCL2</i> (AR) Others	Decreased	Decreased	Myopathy and cardiomyopathy ( <i>LMNA</i> ) Pseudoacromegaly ( <i>PPARG</i> ) SHORT syndrome with partial lipodystrophy, insulin resistance and diabetes ( <i>PIK3R1</i> )	
Partial lipodystrophy	<i>LMNA</i> , <i>PPARG</i> , <i>PIK3R1</i> (AD) Others		Variable		
Complex syndromes	Alström	<i>ALMS1</i> (AR)			
	Bardet–Biedl	<i>BBS1</i> to <i>BBS18</i> (mostly AR)			
	DNA damage repair disorders	<i>WRN</i> (AR) <i>BLM</i> (AR)			
	Primordial dwarfism	<i>PCNT</i> (AR)			

AD, autosomal dominant; AR, autosomal recessive; HDL, high-density lipoprotein; SHORT, short stature, hypermobility of joints, ocular depression, Rieger’s anomaly, and teething delay syndrome.

Primary insulin signaling defects due to mutations in the insulin receptor gene

Insulin receptor (*INSR*) gene mutations are responsible for a number of rare insulin resistance syndromes (155). Leptin levels are low, but adiponectin levels are normal or elevated as insulin normally inhibits adiponectin secretion. The most common form is type A insulin resistance syndrome, which is usually diagnosed in non-obese female adolescents with severe acanthosis nigricans and hyperandrogenism (polycystic ovarian syndrome) and may show autosomal dominant or autosomal recessive inheritance. Mutations in both alleles of *INSR* are also responsible for the more severe Donohue syndrome (formerly known as Leprechaunism) and Rabson–Mendenhall syndrome. The presenting complaint is failure to thrive, with impaired linear growth and weight gain, associated to overgrowth of soft tissues. Postprandial hyperglycemia may be severe but is usually accompanied by fasting hypoglycemia.

Metabolic control in patients with *INSR* mutations remains poor and long-term diabetes complications are frequent. Insulin sensitizers may be tried initially but most patients need extraordinarily high doses of insulin, with limited effect (155). As an alternative therapeutic method for young children, recombinant human insulin-like growth factor (IGF-I) has been reported to improve both fasting and postprandial glycemia although long-term effects on survival remain unclear (156).

Monogenic lipodystrophies

Lipodystrophies are characterized by a selective lack of adipose tissue, which results in decreased adipokines

levels and insulin resistance (157). Mutations in either *AGPAT2* or *BSCL* account for approximately 80% of cases of congenital generalized lipodystrophy (Berardinelli–Seip syndrome) (158). This is a recessive disorder characterized by an almost complete absence of subcutaneous and visceral fat with abdominal distention due hepatic steatosis, which may evolve to hepatic fibrosis. Diabetes usually becomes apparent in early adolescence. In contrast, familial partial lipodystrophy is usually recognized after puberty in patients with loss of subcutaneous fat from the extremities and lower trunk and progressive accumulation of subcutaneous adipose tissue in the face and around the neck. Visceral fat is greatly increased. In addition to hyperinsulinemia, hypertriglyceridemia, and decreased high-density lipoprotein (HDL) cholesterol, patients also show signs of hyperandrogenism and sometimes pseudoacromegalic growth of soft tissues. Diabetes usually appears in late adolescence or early adulthood. Heterozygous mutations in *LMNA* or *PPARG* account for approximately 50% of cases (157). Two recent causes of lipodystrophy and multi-system disease are: (i) subcutaneous lipodystrophy and diabetes, deafness, mandibular hypoplasia, and hypogonadism in males associated with a specific mutation in *POLD1*, a universal DNA polymerase (159) and (ii) SHORT (short stature, hypermobility of joints, ocular depression, Rieger’s anomaly, and teething delay) syndrome with partial lipodystrophy, in which IR and diabetes were caused by a hot spot mutation in *PIK3R1* encoding p85 that has a central role in the insulin-signaling pathway (160).

Dietary advice with a low-fat, sometimes hypocaloric diet is the mainstay of treating lipodystrophies as it can have a dramatic effect on metabolic derangements.

In partial lipodystrophy, insulin sensitizers such as metformin and glitazones may be initially effective (161) but glitazones can cause further accumulation of fat in the face and neck (154). Patients with severe congenital lipodystrophy greatly benefit from treatment with recombinant leptin (162). In partial lipodystrophy, leptin replacement has limited value with improvement of hypertriglyceridemia but not hyperglycemia (163).

#### Ciliopathy-related insulin resistance and diabetes

*Alström syndrome (ALMS)*. This autosomal recessive disorder shares symptoms with Bardet–Biedl syndrome (BBS) (see below), including progressive visual impairment related to cone–rod dystrophy, sensorineural hearing loss, obesity, and diabetes mellitus. It can be distinguished from the latter syndrome by the lack of polydactyly and hypogonadism and by the absence of cognitive impairment (164). More than 60% of individuals with ALMS develop cardiomyopathy. The syndrome is caused by mutations within the *ALMS1* gene of unknown function (165). Patients ALMS usually show many features of the metabolic syndrome including acanthosis nigricans, hyperlipidemia, hyperuricemia, hypertension, and slowly progressive insulin-resistant diabetes (166). Lifestyle intervention can initially ameliorate the metabolic abnormalities (167).

*Bardet–Biedl syndrome*. This disorder is characterized by intellectual disability, progressive visual impairment due to cone–rod dystrophy, polydactyly, obesity, diabetes mellitus, renal dysplasia, hepatic fibrosis, and hypogonadism. Obesity is found in almost every patient, while diabetes affects less than 50% (168). While the syndrome shares some similarities with Lawrence–Moon syndrome, these two disorders can be distinguished by the presence of paraplegia and the absence of polydactyly, obesity, and diabetes mellitus in Lawrence–Moon syndrome. Terms such as Lawrence–Moon–Bardet–Biedl or Lawrence–Moon–Biedl syndrome should therefore be avoided. BBS has been linked to 18 different genetic loci, referred to as *BBS1* to *BBS18* (169, 170). The majority of cases are autosomal recessive (171), but triallelic inheritance has been reported (172). Genetic diagnostic laboratories and detailed clinical recommendations for patients with ALMS and BBS are present at <http://www.euro-wabb.org>.

#### Conclusions

Advances in molecular genetics have led to the identification of genes associated with many clinically identified subgroups of diabetes. Molecular genetic

testing is being used as a diagnostic tool that can help define the diagnosis and treatment of children with diabetes. As these tests are expensive, diagnostic genetic testing should be limited to those patients who are likely to harbor a mutation on clinical grounds.

#### Conflicts of interest

The authors have declared no conflicts of interest.

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