



ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents

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1 | WHAT IS NEW

- Description of additional subtypes of monogenic diabetes
- More data on long-term durability and safety, including an absence of severe hypoglycemia, for sulfonylurea treatment in (K_{ATP})-related neonatal diabetes (KATP-NDM)
- Chromosome 6 linked neonatal diabetes is amenable to sulfonylurea treatment
- Next-generation sequencing (NGS) enables the simultaneous analysis of multiple genes at a lower cost and has already become a feasible alternative to traditional genetic testing
- Variants identified through genetic testing should be classified according to the 2015 American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines

2 | RECOMMENDATIONS

- Monogenic diabetes is uncommon, accounting for approximately 1% to 6% of pediatric diabetes patients (**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 for example, pancreatic exocrine failure and developmental delay (B).

- The diagnosis of 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 more than 5 years after diagnosis [stimulated C-peptide >200 pmol/L]) and lack the characteristics of type 2 diabetes (marked obesity, acanthosis nigricans).
 - Mild stable fasting hyperglycemia which does not progress. Such cases should be tested for glucokinase gene mutations (GCK-MODY), 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 α (HNF1A) gene (HNF1A-MODY) should be considered as the first diagnostic possibility, while mutations in the glucokinase gene (GCK-MODY) 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, because 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, where 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.
- Establishing the correct molecular diagnosis of MODY avoids misdiagnosis as type 1 or type 2 diabetes; may offer more accurate prognosis of the risk of complications; may avoid stigma and limitation of employment opportunity (especially in the case of GCK-MODY); and enables prediction of risk in a first degree relative (unless it is a *de novo* mutation) or in an offspring.

3 | 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 (ie, not inherited from parents). 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 type 2 diabetes and the newly recognized subtype of

familial diabetes became known by the acronym MODY (maturity-onset diabetes of the young).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 β -cells.¹ Over the last few years, however, a number of forms of monogenic diabetes clinically and genetically different from MODY have been identified.⁵ Patients may harbor dominant mutations arising *de novo*; in such cases, family history suggesting a monogenic condition is lacking.⁶⁻⁸ 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^{9,10} or type 2 diabetes.^{11,12} Although monogenic diabetes is uncommon, it accounts for 1% to 6% of pediatric diabetes cases.¹³⁻¹⁸

4 | 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 family members with diabetes or hyperglycemia who may also carry a causal mutation, thereby improving classification of diabetes.

4.1 | Selecting candidates for molecular testing

In contrast to type 1 and type 2 diabetes, where there is no single diagnostic genetic 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 (eg, www.diabetesgenes.org; <http://monogenicdiabetes.uchicago.edu>; <http://www.pediatrics.umed.pl/team/en/contact>; www.mody.no; <http://www.euro-wabb.org/en/european-genetic-diagnostic-laboratories>).

NGS enables the simultaneous analysis of multiple genes at a lower cost per gene and has already replaced much single gene testing by Sanger sequencing or other methods.¹⁹⁻²³ Such NGS panels provide an efficient means of comprehensive testing; however, because they are still expensive it remains appropriate to use a judicious approach to selecting patients for molecular testing. Moreover, some NGS panels include genes lacking robust evidence for a causal role in monogenic diabetes and this can result in a misdiagnosis with adverse consequences for the patient and any family members who undergo

cascade testing. In NDM, genetic testing is actually cost-saving because of improved cheaper treatment; testing for MODY in appropriate populations can also be cost-effective.^{24,25} Thus, comprehensive testing on appropriately selected patients is an increasingly cost-effective approach that can provide a genetic diagnosis that predicts the best diabetes treatment, as well as the development of related features.²⁶ Targeted gene sequencing may still be appropriate for some patients, for example, a pregnant patient with mild fasting hyperglycemia, in whom a rapid test to identify a *GCK* mutation will inform management of the pregnancy. For most patients suspected to have monogenic diabetes, NGS provides an optimal approach for clinical care as it provides a genetic diagnosis that often precedes development of additional clinical features, informs prognosis and guides clinical management.^{24–26}

4.2 | 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), or consider NDM if diagnosis between 6 and 12 months if there is no evidence of autoimmunity or if the patient has other features such as congenital defects, or unusual family history.^{2,27}
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 β -cell function, with low insulin requirements and detectable C-peptide (either in blood or urine) over an extended partial remission phase (at least 5 years after diagnosis).

4.3 | 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. Because there is no specific test for type 2 diabetes and because obesity has become so common in children, patients with monogenic diabetes may also be obese and can be very difficult to distinguish from type 2 diabetes. 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. Family history of diabetes in one parent and other first-degree relatives of that affected parent, especially if any family member with diabetes is not obese.
4. Unusual distribution of fat, such as central fat with thin or muscular extremities.

4.4 | 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. The way the clinician interprets the genetic report will have a major effect on the future 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.²⁸ This includes the method used for mutation screening, limitations of the test, classification of the variant as pathogenic/likely pathogenic or of uncertain significance (with supporting evidence included where appropriate), and information about the likelihood of the disease being inherited by the offspring. The laboratory reporting the results should adhere to the ACMG/AMP variant classification guidelines.²⁹ Referral to a specialist unit (diabetes genetics or clinical genetics) is recommended, where predictive testing of asymptomatic individuals is requested. When testing reveals a variant of uncertain significance, consultation with an expert center with experience in monogenic diabetes can often provide additional insight on the interpretation and recommendations of how to proceed.

5 | SPECIFIC SUBTYPES OF MONOGENIC DIABETES AND THEIR MANAGEMENT

In children, the majority of cases of monogenic diabetes result from mutations in genes causing β 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 extra-pancreatic features (such as congenital heart or gastrointestinal defects, brain malformations, severe diarrhea, or other autoimmune conditions from a very young age, to name a few).
4. Monogenic insulin resistance syndromes (see below: characterized by high insulin levels or high insulin requirements; abnormal distribution of fat with a lack of subcutaneous fat, especially in extremities; dyslipidemia, especially high triglycerides; and/or significant acanthosis nigricans).

6 | NDM DIABETES DIAGNOSED WITHIN THE FIRST 6 TO 12 MONTHS OF LIFE

The clinical presentation of autoimmune type 1 diabetes is exceedingly rare before age 6 months.^{27,30} Even though autoantibodies against β -cell antigens may be occasionally found in very young diabetic infants,²⁷ it is now accepted that mutations in a range of genes related to immune function (such as *FOXP3*, *STAT3*, or *LRBA*) and not

type 1 diabetes, will account for most of these cases.^{31–33} Therefore, all patients diagnosed under 6 months should have genetic testing for monogenic NDM. Some cases of NDM can be diagnosed between 6 and 12 months^{34,35} although the vast majority of these patients have type 1 diabetes. Reasons to consider genetic testing in those diagnosed between 6 and 12 months include: negative autoantibody testing, extra-pancreatic features such as gastrointestinal anomalies or congenital defects, unusual family history, or even the development of multiple autoimmune disorders at a young age (suggesting the possibility of a monogenic cause of autoimmunity such as *FOXP3*, which can occur after 6 months of age in some cases).

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. 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 (TNDM), although it might relapse later in life. In both situations, diabetes presents more frequently isolated, or is the first feature to be noted. Some patients show a variety of associated extra-pancreatic clinical features that may point to a particular gene; however, because these features often are not apparent initially, they will not always be helpful in guiding genetic testing and instead, early comprehensive testing will often allow for the genetic testing result to precede the recognition of other features (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,^{36,37} with activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K_{ATP}) channel of the β -cell membrane (*KCNJ11* or *ABCC8*) causing the majority of the remaining cases (KATP-NDM).³⁸ A minority of cases of TNDM is caused by mutations in other genes, including *HNF1B*,³⁹ *INS*,⁴⁰ etc. In contrast, the genetic abnormality responsible for up to 20% of PNDM cases remains unknown, although the commonest known cause in outbred populations is mutations in the K_{ATP} channel or *INS* genes.^{26,41} If parents are related, Wolcott-Rallison syndrome or homozygous mutations in the *GCK* gene are the most common etiologies.⁴²

6.1 | 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 NDM and always result in TNDM.⁴³ 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,⁴⁴ 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).⁴⁵ 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.⁴⁶ 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.⁴⁷

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.^{45,48} 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 weeks. One third of patients show macroglossia and, more rarely, an umbilical hernia is present. Following remission, a low proportion of patients will exhibit clinically significant hypoglycemia that in some cases requires long-term treatment.^{49,50} During remission, transient hyperglycemia may occur during intercurrent illnesses.⁵¹ Over time, diabetes relapses in at least 50% to 60% of patients and even in more than 85% in one large cohort,⁵² usually around puberty, although recurrences have been reported as young as 4 years of age. Relapse clinically resembles early-onset type 2 diabetes and is characterized by a loss of the first-phase insulin secretion. Because most cases exhibit some degree of endogenous β -cell function, insulin therapy is not always necessary and these patients may respond to oral sulfonylureas or other drugs used for type 2 diabetes^{53–55}.

The phases described above do not present irremediably in every patient. Interestingly, some carrier relatives develop type 2 diabetes or gestational diabetes in adulthood without any evidence of having had NDM, as well as in a small fraction of patients with early-onset, non-obese, and non-autoimmune diabetes without a history of NDM. This suggests significant variability in phenotype, possibly related to other genetic or epigenetic factors that may influence the clinical expression alterations of chromosome 6q24.^{36,56}

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, affected newborn males have a 50% chance as adults of transmitting the mutation and the disease to their children. In contrast, newborn affected females will as adults 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 (ie, *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.

6.2 | Neonatal diabetes due to mutations in the K_{ATP} channel genes (KATP-NDM)

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.⁵⁷ They regulate insulin secretion by linking intracellular metabolic state to the β -cell membrane electrical activity. Any increase in the intracellular metabolic activity induces an increase in the ATP/ADP ratio within the pancreatic β -cell which makes the K_{ATP} channels close, and leads to the cell membrane depolarization which ultimately triggers insulin secretion.⁵⁸ Activating mutations in *KCNJ11* or *ABCC8*, which prevent K_{ATP}

TABLE 1 Monogenic subtypes of neonatal and infancy-onset diabetes (modified from Ref. [42])

Gene	Locus	Inheritance	Other clinical features	Reference
Abnormal pancreatic development				
<i>PLAGL1/HYMAI</i>	6q24	Variable (<i>imprinting</i>)	TNDM ± macroglossia ± umbilical hernia	36
<i>ZFP57</i>	6p22.1	Recessive	TNDM (multiple hypomethylation syndrome) ± macroglossia ± developmental delay ± umbilical defects ± congenital heart disease	47
<i>PDX1</i>	13q12.1	Recessive	PNDM + pancreatic agenesis (steatorrhea)	200
<i>PTF1A</i>	10p12.2	Recessive	PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction	201
<i>PTF1A enhancer</i>	10p12.2	Recessive	PNDM + pancreatic agenesis without central nervous system (CNS) features	108
<i>HNF1B</i>	17q21.3	Dominant	TNDM + pancreatic hypoplasia and renal cysts	39
<i>RFX6</i>	6q22.1	Recessive	PNDM + intestinal atresia + gall bladder agenesis	202
<i>GATA6</i>	18q11.1-q11.2	Dominant	PNDM + pancreatic agenesis + congenital heart defects + biliary abnormalities	109
<i>GATA4</i>	8p23.1	Dominant	PNDM + pancreatic agenesis + congenital heart defects	203
<i>GLIS3</i>	9p24.3-p23	Recessive	PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts	204
<i>NEUROG3</i>	10q21.3	Recessive	PNDM + enteric anendocrinosis (malabsorptive diarrhea)	205
<i>NEUROD1</i>	2q32	Recessive	PNDM + cerebellar hypoplasia + visual impairment + deafness	206
<i>PAX6</i>	11p13	Recessive	PNDM + microphthalmia + brain malformations	207
<i>MNX1</i>	7q36.3	Recessive	PNDM + developmental delay + sacral agenesis + imperforate anus	19
<i>NKX2-2</i>	20p11.22	Recessive	PNDM + developmental delay + hypotonia + short stature + deafness + constipation	32
Abnormal β-cell function				
<i>KCNJ11</i>	11p15.1	Spontaneous or dominant	PNDM/TNDM ± DEND	6
<i>ABCC8</i>	11p15.1	Spontaneous, dominant or recessive	TNDM/PNDM ± DEND	59
<i>INS</i>	11p15.5	Recessive	Isolated PNDM or TNDM	40
<i>GCK</i>	7p15-p13	Recessive	Isolated PNDM	102
<i>SLC2A2 (GLUT2)</i>	3q26.1-q26.3	Recessive	Fanconi-Bickel syndrome: PNDM + hypergalactosemia, liver dysfunction	208
<i>SLC19A2</i>	1q23.3	Recessive	Roger syndrome: PNDM + thiamine-responsive megaloblastic anemia, sensorineural deafness	209
Destruction of β cells				
<i>INS</i>	11p15.5	Spontaneous or dominant	Isolated PNDM	8
<i>EIF2AK3</i>	2p11.2	Recessive	Wolcott-Rallison syndrome: PNDM + skeletal dysplasia + recurrent liver dysfunction	96
<i>IER3IP1</i>	18q21.2	Recessive	PNDM + microcephaly + lissencephaly + epileptic encephalopathy	210
<i>FOXP3</i>	Xp11.23-p13.3	X-linked, recessive	IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, and elevated IgE)	211
<i>WFS1</i>	4p16.1	Recessive	PNDM ^a + optic atrophy ± diabetes insipidus ± deafness	149
<i>WFS1</i>	4p16.1	Dominant	PNDM or infancy-onset diabetes + congenital cataracts + deafness	212

Abbreviations: DEND, developmental delay, epilepsy, and neonatal diabetes mellitus; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, and X-linked; TNDM, transient neonatal diabetes mellitus.

^a The mean age of diagnosis among patients with *WFS1* mutations is approximately 5 years.¹⁵⁴

channel closure and hence insulin secretion in response to hyperglycemia, are the most common cause of PNDM^{6,59–62} (Figure 1) and the second most common cause of TNDM.³⁸ A loss-of-function nonsense mutation in *ABCC8*, resulting in gain-of-channel function, has also been reported.⁶³

The majority of patients with mutations in *KCNJ11* have PNDM rather than TNDM (90% vs 10%). In contrast, mutations in *ABCC8* cause TNDM more frequently (approximately 66%).^{59,64} There are no

significant differences between the two subtypes of NDM regarding the severity of intrauterine growth retardation or the age at diagnosis of diabetes.³⁸ 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.³⁸

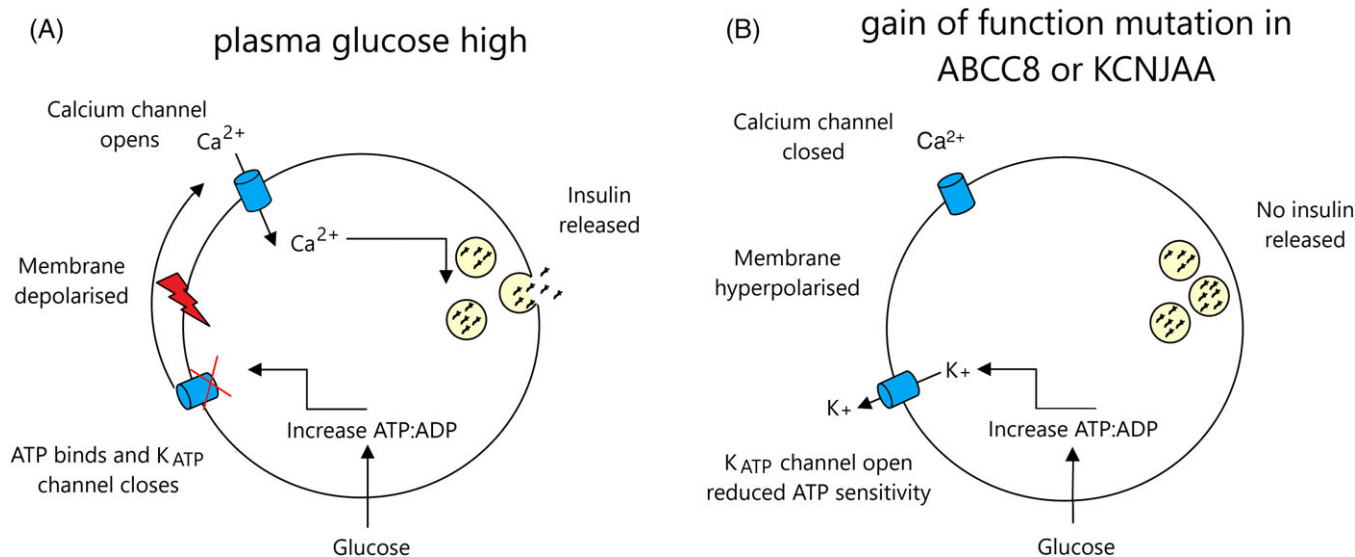


FIGURE 1 Insulin secretion from the pancreatic beta cell in (A) normal cell in a high plasma glucose environment and (B) in a cell with a K -ATP channel mutation—adapted from Ref. 199. A, Glucose enters the cell and is metabolized, causing an increase in ATP, K -ATP channel closure is induced via ATP binding, the membrane is depolarized and calcium influx is triggered resulting in the release of insulin from its storage vesicles. B, A gain of function mutation in the K -ATP channel results in the failure of ATP to bind to the channel, causing the channel to remain open, the membrane stays hyperpolarized and no insulin is released

Presenting clinical features in patients with K_{ATP} -NDM suggest insulin dependency, with low or undetectable C-peptide levels and frequent presentation with diabetic ketoacidosis⁶⁵. In addition to diabetes, about 20% of patients with mutations in *KCNJ11* were initially found to present with associated neurological features^{6,66,67} in keeping with the expression of K_{ATP} channels in neurons and muscle cells.^{58,68} The most severely damaging mutations are also associated with marked developmental delay and early-onset epilepsy and became known as DEND (developmental delay, epilepsy, and NDM) syndrome. An intermediate DEND syndrome characterized by neonatal diabetes and less severe developmental delay without epilepsy is more common. Neurological features have been reported less frequently in patients with mutations in *ABCC8*.^{59,60} Recent studies utilizing detailed testing have revealed that mild neurodevelopmental abnormalities occur even in those with milder mutations previously thought to cause only isolated diabetes. With some studies using sibling controls, mild but significant impairments were found in several domains including IQ, measures of academic achievement and executive function. Many patients met criteria for developmental coordination disorder (particularly visual-spatial dyspraxia), attention deficit hyperactivity disorder, anxiety disorder, or autism, and/or had behavioral or sleep difficulties.^{52,69–72}

Approximately 90% of patients with activating mutations in the K_{ATP} channel genes can be transferred from insulin onto off-label sulfonylurea tablets,^{73,74} and personal communication from Jacques Bertrand MD PhD (Necker University Hospital, France). In 2018 a pharmaceutical grade suspension of glibenclamide developed for children was given market authorization in the European Union.⁷⁵ Treatment with sulfonylurea dramatically improves glycemic control and appears to be durable over the long-term with only minimal hypoglycemia that is not severe.^{76,77} The doses required are high when calculated on a per kg body weight basis compared to adults with type

2 diabetes, typically needing around 0.5 mg/kg/day of glibenclamide, although doses as high as 2.3 mg/kg/day have been occasionally been reported.^{78,79} The dose required depends mostly on the age at which the patient starts sulfonylurea, as well as the specific mutation.^{80,81} Many patients have been able to progressively reduce the dose of sulfonylurea after transition while maintaining excellent glycemic control.^{73,82} The only side effects reported to date are transient diarrhea and staining of the teeth.^{83,84} Some brain imaging studies have shown that sulfonylurea drugs may penetrate blood-brain barrier, but maintenance of levels may limit benefit.^{85–87} Many interesting case reports suggest that sulfonylureas may partially improve some of the neurological symptoms, but the degree of improvement possible may also depend on how early treatment is started.^{88–91}

Activating mutations in *KCNJ11* causing NDM are always heterozygous. Because about 90% of these mutations arise *de novo*, there is usually no family history of NDM⁹² 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 NDM is recessively inherited.⁶⁰ In this case, the risk of NDM for future siblings is 25% but almost non-existent for the offspring of the affected patient. Germline mosaicism (mutations present in the gonads but not detectable in blood) has been reported in several families⁹² 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.

6.3 | Neonatal diabetes due to mutations in *INS* gene

Heterozygous coding mutations in the preproinsulin gene (*INS*) are the second most common cause of PNDM after K_{ATP} channel mutations.^{8,93,94} The mutations usually result in a misfolded proinsulin

molecule that is trapped and accumulated in the endoplasmic reticulum, leading to endoplasmic reticulum stress and β -cell apoptosis.

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.⁹³

The majority of heterozygous *INS* mutations are sporadic *de novo* mutations. Only about 20% of probands have a positive family history of autosomal dominant NDM.⁹³ 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.^{94,95}

In addition to heterozygous *INS* mutations, homozygous or compound heterozygous mutations causing NDM have also been described.⁴⁰ Biallelic mutations do not cause slowly progressive β -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. Because 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.

6.4 | Wolcott-Rallison syndrome

Biallelic mutations in *EIF2AK3* cause a rare autosomal recessive syndrome characterized by early-onset diabetes mellitus, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction.^{96,97} *EIF2AK3* (eukaryotic translation initiation factor alpha 2-kinase 3) 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 β -cell apoptosis. Although diabetes usually manifests during infancy, it might not present until 3 to 4 years 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.^{98,99} Because 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.

6.5 | Neonatal diabetes due to GCK mutations

The enzyme glucokinase is considered the glucose sensor of the β -cells, as it catalyzes the rate-limiting step of glucose phosphorylation and therefore enables the β -cell to respond appropriately to the degree of glycemia.¹⁰⁰ 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 β -cells from secreting insulin in response to hyperglycemia.^{101,102} 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% to 3% of cases of PNDM overall.⁴² 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 NDM, even when there is no known consanguinity or family history of diabetes, is often recommended. Sulfonyleurea treatment has been tested with no clear effect (P.R.N., A.T.H. unpublished observations).

6.6 | IPEX syndrome

Mutations in the *FOXP3* gene are responsible for the immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome.^{103,104} This is the only well-established form of PNDM that is associated with β -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.^{105,106} Alternatively, allogeneic bone marrow transplantation with reduced-intensity conditioning should be considered.¹⁰⁷

6.7 | Other causes of neonatal diabetes

More than >30 genetic subtypes of neonatal diabetes have been described. The clinical features seen in the more common 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.^{108,109} Apart from *KATP*-NDM and some patients with *SLC19A2* mutations causing thiamine-responsive megaloblastic anemia (TRMA) syndrome,¹¹⁰ all other causes need to be treated with subcutaneous insulin. Patients with pancreatic aplasia/hypoplasia will also require exocrine pancreatic supplements.

6.8 | 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.¹¹¹ 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.

7 | AUTOSOMAL DOMINANT FAMILIAL MILD HYPERGLYCEMIA OR DIABETES (MODY)

MODY syndromes are forms of monogenic diabetes characterized by impaired insulin secretion, with minimal or no defects in insulin action.¹¹² The different genetic subtypes of MODY differ in age of onset, pattern of hyperglycemia, and response to treatment. Most cause isolated diabetes and therefore may be misdiagnosed as either familial type 1 or type 2 diabetes.^{11,113} Although the classic criteria for MODY include family history of diabetes, sporadic *de novo* mutations in a number of causative genes have been reported.¹¹⁴

Three genes are responsible for the majority of MODY cases (GCK, HNF1A, and HNF4A) and will be described in some detail below. However, at least 14 different genes have been reported to cause diabetes with a MODY-like phenotype (Table 2), and some panels will include all of these genes, or possibly also many other genes associated with exceedingly rare recessive causes. In the modern era of expanded testing by many different laboratories, caution must be used when interpreting test results, as often there is very little information available to support the causality of rare variants in uncommon subtypes. Most MODY subtypes will have a phenotype of isolated diabetes or stable mild fasting hyperglycemia, but some MODY genes have additional features such as renal cysts (see HNF1B below) or pancreatic exocrine dysfunction.¹¹⁵

7.1 | 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 minimal¹¹⁶ and a significant proportion will have a heterozygous mutation in GCK.¹¹⁷ 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.¹¹⁸ Their HbA1c is mildly elevated but usually below 7.5%.¹¹⁹ 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),¹²⁰ although this should not be considered an absolute criterion because of the variability of the oral glucose tolerance test (OGTT). Because 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 GCK mutation. GCK-MODY may first be diagnosed during pregnancy; it represents approximately 2% to 6% of cases of gestational diabetes and can be differentiated from gestational diabetes on the basis of clinical characteristics and fasting glucose.^{121,122}

Because blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely associated with chronic microvascular or macrovascular complications of diabetes^{123,124} and patients do not generally require any treatment¹²⁵ except in the setting of pregnancy where an affected mother has an unaffected fetus and there is *in utero* evidence of accelerated growth.¹²⁶ 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.¹²⁷ GCK-PNDM may manifest in GCK-MODY families especially in the setting of consanguinity.

7.2 | 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.¹²⁸ Therefore, HNF1A-MODY is the first diagnostic possibility to be considered in families with autosomal dominant symptomatic diabetes.

In both HNF1A- 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 hours during an OGTT.¹²⁰ Patients with HNF1A-MODY demonstrate impaired incretin effect and inappropriate glucagon responses to OGTT.¹²⁹ Over time, fasting hyperglycemia and osmotic symptoms (polyuria, polydipsia) present but patients rarely develop ketosis because some residual insulin secretion persists for many years. Chronic complications of diabetes are

TABLE 2 Common subtypes of MODY and associated clinical features

Gene	Locus	Clinical features	Treatment	References
HNF4A	20q12-q13.1	Macrosomia and neonatal hypoglycemia, renal Fanconi syndrome (mutation specific)	Sulfonylurea	213
GCK	7p15-p13	Mild asymptomatic hyperglycemia	Nil/diet	214
HNF1A	12q24.2	Renal glycosuria	Sulfonylurea	215
HNF1B	17q12	Renal developmental abnormalities, genital tract malformations	Insulin	216

Abbreviation: MODY, maturity-onset diabetes of the young.

frequent and their development is related to the degree of metabolic control.¹³⁰ 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 and retinopathy.¹³¹

Mutations in *HNF1A* show a high penetrance so that 63% of mutation carriers develop diabetes before 25 years of age, 79% before age 35 and 96% before 55 years.⁵ The age at diagnosis of diabetes is partly determined by the location of the mutation within the gene.^{132,133} Patients with mutations affecting the terminal exons 8 to 10 are diagnosed, on average, 8 years later than those with mutations in exons 1 to 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 years.¹²⁰ In the pediatric population, diabetes in *HNF4A* mutation carriers tend to appear at a similar age to patients with mutations in *HNF1A*.¹⁵

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.¹³⁴
- In addition to diabetes, carriers of the p.Arg76Trp (R76W) mutation in *HNF4A* present with an atypical form of Fanconi syndrome including hypercalciuria and nephrocalcinosis.¹³⁵
- About 50% of *HNF4A* mutation carriers are macrosomic at birth and 15% have diazoxide-responsive neonatal hyperinsulinemic hypoglycemia.¹³⁶ In this case, hyperinsulinism typically remits during infancy and patients develop diabetes from adolescence.^{137,138} Hyperinsulinemic hypoglycemia has also been reported in *HNF1A* mutation carriers¹³⁹ but this is very uncommon.

Patients with both *HNF1A* and *HNF4A*-diabetes can initially be treated with diet although they will have marked postprandial hyperglycemia with high carbohydrate food.¹²⁰ Most patients will need pharmacological treatment as they show progressive deterioration in glycemic control. They are extremely sensitive to sulfonylureas,¹⁴⁰ which usually allow a better glycemic control than that achieved on insulin, especially in children and young adults.¹⁴¹ 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 (eg, 20-40 mg gliclazide daily) for decades.^{142,143} 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 a meglitinide may be considered.¹⁴⁴ A 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.¹⁴⁵

8 | GENETIC SYNDROMES ASSOCIATED WITH DIABETES

A monogenic disorder should be considered in any child with diabetes associated with multi-system extrapancreatic features.¹⁴⁶ These syndromes may either cause NDM (Table 1) or present later in life (see below). The Online Mendelian Inheritance in Man website (www.ncbi.nlm.nih.gov/omim or 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.¹⁴⁷ The most common syndromes usually presenting beyond infancy are described in some detail below. A number of rare syndromes that include diabetes may also be tested through a gene panel approach (eg, see <https://www.diabetesgenes.org/>).

8.1 | Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) syndrome (Wolfram syndrome, WFS)

The association of diabetes with progressive optic atrophy below 16 years of age is diagnostic of this autosomal recessive syndrome.¹⁴⁸ Non-autoimmune diabetes is usually the first manifestation of the disease and presents at a mean age of 6 years, although may present anytime from early-infancy.¹⁴⁹ Patients require insulin treatment from diagnosis. Other typical clinical features, such as sensorineural deafness, central diabetes insipidus, urinary tract dysfunction, and neurological symptoms develop later in a variable order even within the same family.¹⁵⁰⁻¹⁵² Many patients with WFS are initially diagnosed as having type 1 diabetes; subsequent loss of vision, which occurs approximately 4 years after diabetes diagnosis, may be misdiagnosed as diabetic retinopathy.^{153,154} Patients with WFS die at a median age of 30 years, mainly from neurodegenerative complications. At least 90% of patients harbor recessively-acting mutations in the *WFS1* gene.¹⁵⁵ A second variant of the syndrome (WFS2) has been described in association with mutations in *CISD2*.¹⁵⁶ Patients with this rare variant do not develop diabetes insipidus but present with additional symptoms including bleeding diathesis and peptic ulcer disease.

8.2 | Renal cysts and diabetes (RCAD) 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.¹⁵⁷ In contrast, renal developmental disorders (especially renal cysts and renal dysplasia) are present in almost all patients with *HNF1B* mutations or gene deletions⁷ and constitute the main presentation in children, even in the absence of diabetes.¹⁵⁸ Genital-tract malformations (particularly uterine abnormalities), hyperuricemia, and gout can also occur, as well as abnormal liver function tests.¹⁵⁷ Diabetes develops later, typically during adolescence or early adulthood,^{159,160} although TNDM has been reported in a few cases.^{39,161} In addition to insulin deficiency related to pancreatic hypoplasia,¹⁶² patients also show some degree of hepatic insulin resistance,¹⁶³ which explains why they do not respond

adequately to sulfonylurea treatment and require early insulin therapy.⁵ Moreover, mutation carriers have lower exocrine pancreatic function with reduced fecal elastase; this involves both ductal and acinar cells.¹⁶⁴ Therefore, the phenotype of 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, because the absence of the pancreatic body and/or tail is highly indicative of *HNF1B*-MODY.¹⁶⁵ Fecal elastase should also be measured, as this is always abnormal in patients with *HNF1B*-MODY.¹⁶⁴ Importantly, a family history of renal disease or diabetes is not essential to prompt genetic testing, as *de novo* mutations and deletions of this gene are common (one-third to two-thirds of cases).^{7,158}

8.3 | Mitochondrial diabetes

Diabetes due to mitochondrial mutations and deletions is rarely seen (<1%) in children and adolescents¹⁶⁶ 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.¹⁶⁷ Although it typically presents in adulthood, some cases have been reported in adolescents with a high degree of heteroplasmy.^{166,168,169} Mitochondrial diabetes should be suspected in patients presenting with diabetes and sensorineural hearing loss inherited from mother's side, or diabetes and progressive external ophthalmoplegia. Interestingly, the same m.3243A>G mutation also causes a much more severe clinical syndrome known as MELAS (myopathy, encephalopathy, lactic acidosis, and stroke).¹⁷⁰

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.¹⁷¹

The penetrance of diabetes in mutation carriers depends on the age considered, but is estimated to be above 85% at 70 years.¹⁶⁷ 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.⁵ 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 syndrome¹⁷² and Pearson syndrome.¹⁷³

8.4 | 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.¹¹⁵ Importantly, the exocrine component of the syndrome is initiated already in childhood, 10 to 30 years before diabetes develops, and can be revealed by lowered fecal elastase and/or pancreatic lipomatosis.^{174,175} Other autosomal dominant monogenic diseases affecting mainly the exocrine pancreas that can lead to diabetes sooner or later include cystic fibrosis (*CFTR*), hereditary

pancreatitis (*PRSS1* and *SPINK1*),¹⁷⁶ and pancreatic agenesis/hypoplasia (*GATA6*).¹⁰⁹

9 | MONOGENIC INSULIN RESISTANCE SYNDROMES

The key features of insulin resistance syndromes include 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.¹⁷⁷ Clinical and biochemical characterization of patients with severe insulin resistance may be used to guide genetic testing, as it happens with monogenic β -cell diabetes (Table 3). However, diabetes associated with monogenic severe insulin resistance is far less common than monogenic β -cell failure, especially in prepubertal children as hyperglycemia is usually a late event in the natural history of these disorders.¹⁷⁸ Because 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.

9.1 | Primary insulin signaling defects due to mutations in the insulin receptor (*INSR*) gene

INSR mutations are responsible for a number of rare insulin resistance (IR) syndromes.¹⁷⁹ Leptin levels are low, but adiponectin levels are normal or elevated because insulin normally inhibits adiponectin secretion. The most common form is type A IR syndrome, which is usually diagnosed in non-obese female adolescents with severe acanthosis nigricans and hyperandrogenism (polycystic ovarian syndrome) and may show autosomal dominant (AD) or autosomal recessive (AR) 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.¹⁷⁹ As an alternative therapeutic method for young children, recombinant human IGF-I has been reported to improve both fasting and postprandial glycemia although long-term effects on survival remain unclear.^{180,181}

9.2 | Monogenic lipodystrophies

Lipodystrophies are characterized by a selective lack of adipose tissue, which results in decreased adipokine levels and insulin resistance.^{182,183} Mutations in either *AGPAT2* or *BSCL* account for

TABLE 3 Classification of syndromes of severe insulin resistance (modified from Ref. [178])

IR syndrome subtype		Gene (inheritance)	Leptin	Adiponectin	Other clinical features
Primary insulin signaling defects	Receptor defect	<i>INSR</i> (AR or AD)	Decreased	Normal or elevated	No dyslipidemia or hepatic steatosis
	Post receptor defects	<i>AKT2</i> , <i>TBC1D4</i> (AD)			Elevated fasting triglycerides and LDL, hepatic steatosis, diabetes (<i>AKT2</i>)
Adipose tissue abnormalities	Monogenic obesity	<i>MC4R</i> (AD) <i>LEP</i> , <i>LEPR</i> , <i>POMC</i> (AR) Others	Increased (low in <i>LEP</i>)		Tall stature (<i>MC4R</i>) Hypogonadism (<i>LEP</i>) Hypoadrenalism (<i>POMC</i>)
	Congenital generalized lipodystrophy	<i>AGPAT2</i> , <i>BSCL2</i> (AR) Others	Decreased	Decreased	Severe dyslipidemia (high triglycerides, low HDL cholesterol) Hepatic steatosis
	Partial lipodystrophy	<i>LMNA</i> , <i>PPARG</i> , <i>PIK3R1</i> (AD) Others	Variable		Myopathy and cardiomyopathy (<i>LMNA</i>) Pseudo-acromegaly (<i>PPARG</i>) SHORT syndrome with partial lipodystrophy, and diabetes (<i>PIK3R1</i>)
Complex syndromes	Alström	<i>ALMS1</i> (AR)			Cone-rod dystrophy leading to blindness, sensorineural hearing loss, diabetes and cardiomyopathy
	Bardet-Biedl	<i>BBS1</i> to <i>BBS18</i> (mostly AR)			Cone-rod dystrophy, obesity, renal dysfunction, polydactyly, learning disabilities, hypogonadism and diabetes
	DNA damage repair disorders	<i>WRN</i> (AR)			Scleroderma-like skin changes, cataracts, increased cancer risk, atherosclerosis and diabetes;
		<i>BLM</i> (AR)			Sun-sensitive, telangiectatic skin changes; increased cancer risk and diabetes
Primordial dwarfism	<i>PCNT</i> (AR)			Microcephalic osteodysplastic primordial dwarfism and diabetes	

approximately 80% of cases of congenital generalized lipodystrophy (Berardinelli-Seip syndrome).¹⁸⁴ 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 HDL cholesterol, patients also show signs of hyperandrogenism and sometimes pseudo-acromegalic 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.¹⁸² Two causes of lipodystrophy and multi-system disease are: (a) subcutaneous lipodystrophy and diabetes, deafness, mandibular hypoplasia, and hypogonadism in males associated with a specific mutation in *POLD1*, a universal DNA polymerase¹⁸⁵ and (b) SHORT syndrome (short stature, hypermobility of joints, ocular depression, Rieger anomaly, and teething delay) with partial lipodystrophy, in which insulin resistance and diabetes were caused by a hot spot mutation in *PIK3R1* encoding p85 that has a central role in the insulin-signaling pathway.¹⁸⁶

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 effective¹⁸⁷ but glitazones can cause further accumulation of fat in the face and neck.¹⁷⁸ Patients with severe congenital lipodystrophy greatly benefit from recombinant leptin, with long-term treatment being well tolerated and resulting in

sustained improvements in hypertriglyceridemia, glycemic control, and liver volume¹⁸⁸. In partial lipodystrophy, leptin replacement has limited value with improvement in hypertriglyceridemia but not hyperglycemia.¹⁸⁹

9.3 | Ciliopathy-related insulin resistance and diabetes

9.3.1 | 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.¹⁹⁰ More than 60% of individuals with ALMS develop cardiomyopathy. The syndrome is caused by mutations within the *ALMS1* gene of unknown function.¹⁹¹ Patients with ALMS usually show many features of the metabolic syndrome including acanthosis nigricans, hyperlipidemia, hyperuricemia, hypertension, and slowly-progressive insulin-resistant diabetes.¹⁹² Lifestyle intervention can initially ameliorate the metabolic abnormalities.¹⁹³

9.3.2 | 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%.¹⁹⁴ 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*^{195,196}. The majority of cases are autosomal recessive,¹⁹⁷ but triallelic inheritance has been reported.¹⁹⁸ Genetic diagnostic laboratories and detailed clinical recommendations for patients with ALMS and BBS are present at <http://www.euro-wabb.org>.

10 | 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. Due to the high likelihood of finding a mutation, molecular genetic testing is recommended at the time of diabetes diagnosis in child aged less than 6 months.

CONFLICTS OF INTEREST

M.P. has acted as scientific advisor for the development of the glibenclamide-glyburide suspension named AMGLIDIA in the European Union. The other authors have declared no conflicts of interest.

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