

The diagnosis and management of monogenic diabetes in children and adolescents

ISPAD 2018 Guidelines

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Pr Michel Polak MD, PhD 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.

What's new

- Description of additional subtypes of monogenic diabetes
- More data on long-term durability and safety, including an absence of severe hypoglycemia, for sulphonylurea treatment in (K_{ATP})-related neonatal diabetes (KATP-NDM)
- Chromosome 6 linked neonatal diabetes is amenable to sulphonylurea 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 ACMG/AMP guidelines

Recommendations

- Monogenic diabetes is uncommon, accounting for ~1–6% 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 6-12 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 sulphonylureas 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 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, since 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 sulphonylureas, 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.

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 (i.e. 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 non-insulin dependent 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 1–6% of pediatric diabetes cases (13-18).

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.

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 (for example, 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 hyperglycaemia, 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)

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 6-12 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).

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.

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 (VUS), consultation with an expert center with experience in monogenic diabetes can often provide additional insight on the interpretation and recommendations of how to proceed.

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).

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 (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 6-12 months (34, 35) although the vast majority of these patients have type 1 diabetes. Reasons to consider genetic testing in those diagnosed between 6-12 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 (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 are 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).

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 nonketotic 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 50-60% 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, 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.

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[SMA1][DM2] 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 (6, 59-62) 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 (~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).

Presenting clinical features in patients with KATP-NDM suggest insulin dependency, with low or undetectable C-peptide levels and frequent presentation with diabetic ketoacidosis (65)]. 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 **are possible occur** even in those with **more 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 **ted** sulfonylurea tablets (73, 74), **and** personal communication **from** Jacques Beltrand MD PhD Necker University Hospital, France). In 2018 a pharmaceutical grade suspension of glibenclamide=glyburide developed for children was given market authorization in the European—union (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004379/human_med_002228.jsp&mid=WC0b01ac058001d124 ; accessed July 8th 2018 [SMA3][DM4]) Treatment with sulphonylurea dramatically improves glycemic control and appears to be durable over the long-term with only minimal hypoglycemia that is not severe (75, 76). 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 (77, 78). The dose required depends mostly on the age at which the patient starts sulphonylurea, as well as the specific mutation (79, 80). Many patients have been able to progressively reduce the dose of sulphonylurea after transition while maintaining excellent glycemic control (73, 81). The only side effects reported to date are transient diarrhea and staining of the teeth (82, 83). Some brain imaging studies have shown that sulphonylurea **drugs** [SMA5][DM6] may penetrate blood-brain barrier, but maintenance of levels may limit benefit (84-86). Many interesting case reports suggest that sulphonylureas may partially improve some of the neurological symptoms, but the degree of improvement possible may also depend on how early treatment is started (87-90).

Activating mutations in *KCNJ11* causing NDM are always heterozygous. Since about 90% of these mutations arise *de novo*, there is usually no family history of NDM (91) 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 families (91) 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 preproinsulin gene (*INS*) are the second most common cause of PNDM after K_{ATP} channel mutations (8, 92, 93). 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 (92).

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 (92). 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 (93, 94).

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. Since 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* cause a rare autosomal recessive syndrome characterized by early-onset diabetes mellitus, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction (95, 96). *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 3-4 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 (97, 98). Since 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 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 (99). 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 (100, 101). 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 (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. Sulphonylurea treatment has been tested with no clear effect (PRN, ATH unpublished observations).

IPEX syndrome

Mutations in the *FOXP3* gene are responsible for the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome (102, 103). 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 (104, 105). Alternatively, allogeneic bone marrow transplantation with reduced-intensity conditioning should be considered (106).

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 (107, 108). Apart from KATP-NDM and some patients with *SLC19A2* mutations causing thiamine-responsive megaloblastic anaemia (TRMA) syndrome (109), 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)

MODY syndromes are forms of Monogenic diabetes characterized by impaired insulin secretion, with minimal or no defects in insulin [action](#)[\[SMA7\]](#)[\[DM8\]](#) (110). 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, 111). Although the classic criteria for MODY include family history of diabetes, sporadic *de novo* mutations in a number of causative genes have been reported (112).

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 {Raeder, 2006 #3020[SMA9][DM10]}.

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 {Lorini, 2001 #7437[SMA11][DM12]} and a significant proportion will have a heterozygous mutation in *GCK* (113). 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 (114). Their HbA1c is mildly elevated but usually below 7.5% (115). 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) (116), although this should not be considered an absolute criterion because of the variability of the OGTT. Since 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 2-6% of cases of gestational diabetes and can be differentiated from gestational diabetes on the basis of clinical characteristics and fasting glucose (117, 118).

Since blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely associated with chronic microvascular or macrovascular complications of diabetes (119, 120) and patients do not generally require any treatment (121) except in the setting of pregnancy where an affected mother has an unaffected fetus and there is *in utero* evidence of accelerated growth (122). 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 (123). *GCK*-PNDM may manifest in *GCK*-MODY families especially in the setting of consanguinity.

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* (124). 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 (116). Patients with *HNF1A*-MODY demonstrate impaired incretin effect and inappropriate glucagon responses to OGTT (125). 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 frequent and their development is related to the degree of metabolic control (126). The frequency of microvascular

complications (retinopathy, nephropathy, 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 (127).

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 (128, 129). 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 (116). 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 (130).
- 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 (131).
- About 50% of *HNF4A* mutation carriers are macrosomic at birth and 15% have diazoxide-responsive neonatal hyperinsulinemic hypoglycemia (132). In this case, hyperinsulinism typically remits during infancy and patients develop diabetes from adolescence (133, 134). Hyperinsulinemic hypoglycemia has also been reported in *HNF1A* mutation carriers (135) 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 (116). Most patients will need pharmacological treatment as they show progressive deterioration in glycemic control. They are extremely sensitive to sulfonylureas (136), which usually allow a better glycemic control than that achieved on insulin, especially in children and young adults (137). 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 (138, 139). 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 (140). 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 (141).

Genetic syndromes associated with diabetes

A monogenic disorder should be considered in any child with diabetes associated with multi-system extrapancreatic features (142). 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 (143). 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 (for example, see <https://www.diabetesgenes.org/>).

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 (144). 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 (145). 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 (146-148). Many patients with WFS are initially diagnosed as having type 1 diabetes; subsequent loss of vision, which occurs approximately four years after diabetes diagnosis, may be misdiagnosed as diabetic retinopathy (149, 150). 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 (151). A second variant of the syndrome (WFS2) has been described in association with mutations in *CISD2* (152). 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 (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 (153). In contrast, renal developmental disorders (especially renal cysts and renal dysplasia) are present in almost all patients with *HNF1B* mutations or gene deletions (154) and constitute the main presentation in children, even in the absence of diabetes (155). Genital-tract malformations (particularly uterine abnormalities), hyperuricemia and gout can also occur, as well as abnormal liver function tests (153). Diabetes develops later, typically during adolescence or early adulthood (156, 157), although TNDM has been reported in a few cases (39, 158). In addition to insulin deficiency related to pancreatic hypoplasia (159), patients also show some degree of hepatic insulin resistance (160), 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 (161). 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, since the absence of the pancreatic body and/or tail is highly indicative of *HNF1B*-MODY (162). Fecal elastase should also be measured, as this is always abnormal in patients with *HNF1B*-MODY (161). 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, 155).

Mitochondrial diabetes

Diabetes due to mitochondrial mutations and deletions is rarely seen (<1%) in children and adolescents (163) 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 (164). Although it typically presents in adulthood, some cases have been reported in adolescents with a high degree of heteroplasmy (163, 165, 166). 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) (167).

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 (168).

The penetrance of diabetes in mutation carriers depends on the age considered, but is estimated to be above 85% at 70 years (164). 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 syndrome (169) and Pearson syndrome (170).

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 (171). Importantly, the exocrine component of the syndrome is initiated already in childhood, 10-30 years before diabetes develops, and can be revealed by lowered fecal elastase and/or pancreatic lipomatosis (172, 173). 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*) (174) and pancreatic agenesis/hypoplasia (*GATA6*) (108).

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 (175). 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 (176). Since 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.

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

INSR mutations are responsible for a number of rare IR syndromes (177). Leptin levels are low, but adiponectin levels are normal or elevated since 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 AD or 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 (177). 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 (178, 179).

Monogenic lipodystrophies

Lipodystrophies are characterized by a selective lack of adipose tissue, which results in decreased adipokine levels and insulin resistance (180, 181). Mutations in either *AGPAT2* or *BSCL* account for approximately 80% of cases of congenital generalized lipodystrophy (Berardinelli–Seip syndrome) (182). 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 (180). Two 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 (183) and (ii) SHORT syndrome (short stature, hypermobility of joints, ocular depression, Rieger's anomaly, 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 (184).

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 (185) but glitazones can cause further accumulation of fat in the face and neck (176). 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 volume (186)]. In partial lipodystrophy, leptin replacement has limited value with improvement in hypertriglyceridemia but not hyperglycemia (187).

Ciliopathy-related insulin resistance and diabetes

Alström syndrome (ALMS)

This autosomal recessive disorder shares symptoms with Bardet-Biedl syndrome (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 (188). More than 60% of individuals with ALMS develop cardiomyopathy. The syndrome is caused by mutations within the *ALMS1* gene of unknown function (189). Patients with Alström syndrome usually show many features of the metabolic syndrome including acanthosis nigricans, hyperlipidemia, hyperuricemia, hypertension, and slowly-progressive insulin-resistant diabetes (190). Lifestyle intervention can initially ameliorate the metabolic abnormalities (191).

Bardet-Biedl syndrome (BBS)

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% (192). 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. Bardet-Biedl syndrome has been linked to 18 different genetic loci, referred to as *BBS1* to *BBS18* (193, 194) The majority of cases are autosomal recessive (195), but triallelic inheritance has been reported (196). 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.

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)	(197)
<i>PTF1A</i>	10p12.2	Recessive	PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction	(198)
<i>PTF1A enhancer</i>	10p12.2	Recessive	PNDM + pancreatic agenesis without CNS features	(107)
<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	(199)
<i>GATA6</i>	18q11.1- q11.2	Dominant	PNDM + pancreatic agenesis + congenital heart defects + biliary abnormalities	(108)
<i>GATA4</i>	8p23.1	Dominant	PNDM + pancreatic agenesis + congenital heart defects	(200)
<i>GLIS3</i>	9p24.3- p23	Recessive	PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts	(201)
<i>NEUROG3</i>	10q21.3	Recessive	PNDM + enteric anendocrinosis (malabsorptive diarrhea)	(202)
<i>NEUROD1</i>	2q32	Recessive	PNDM + cerebellar hypoplasia + visual impairment + deafness	(203)
<i>PAX6</i>	11p13	Recessive	PNDM + microphthalmia + brain malformations	(204)
<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 \pm DEND	(6)
<i>ABCC8</i>	11p15.1	Spontaneous, dominant or recessive	TNDM/PNDM \pm DEND	(59)
<i>INS</i>	11p15.5	Recessive	Isolated PNDM or TNDM	(40)
<i>GCK</i>	7p15-p13	Recessive	Isolated PNDM	(101)
<i>SLC2A2</i> (GLUT2)	3q26.1-q26.3	Recessive	Fanconi-Bickel syndrome: PNDM + hypergalactosemia, liver dysfunction	(205)
<i>SLC19A2</i>	1q23.3	Recessive	Roger's syndrome: PNDM + thiamine-responsive megaloblastic anemia, sensorineural deafness	(206)
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	(95)
<i>IER3IP1</i>	18q21.2	Recessive	PNDM + microcephaly + lissencephaly + epileptic encephalopathy	(207)
<i>FOXP3</i>	Xp11.23-p13.3	X-linked, recessive	IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, elevated IgE)	(208)
<i>WFS1</i>	4p16.1	Recessive	PNDM* + optic atrophy \pm diabetes insipidus \pm deafness	(145)
<i>WFS1</i>	4p16.1	Dominant	PNDM or infancy-onset diabetes + congenital cataracts + deafness	(209)

*The mean age of diagnosis among patients with *WFS1* mutations is approximately 5 years (150)

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 hypoglycaemia, renal Fanconi syndrome (mutation specific)	Sulphonylurea	(210)
<i>GCK</i>	7p15-p13	Mild asymptomatic hyperglycemia	Nil / diet	(211)
<i>HNF1A</i>	12q24.2	Renal glucosuria	Sulphonylurea	(212)
<i>HNF1B</i>	17q12	Renal developmental abnormalities, genital tract malformations	Insulin	(213)

Table 3. Classification of Syndromes of Severe Insulin Resistance (modified from ref (176)).

IR syndrome subtype		Gene (inheritance)	Leptin	Adiponectin	Other clinical features
Primary insulin signalling defects	Receptor defect	<i>INSR</i> (AR or AD)	Decreased	Normal or elevated	No dyslipidemia or hepatic steatosis
	Post receptor defects	<i>AKT2, 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, LEPR, 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, BSCL2</i> (AR) Others	Decreased	Decreased	Severe dyslipidemia (high triglycerides, low HDL cholesterol) Hepatic steatosis
	Partial lipodystrophy	<i>LMNA, PPARG, 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>)
	Alström	<i>ALMS1</i> (AR)			Cone-rod dystrophy

Complex syndromes					leading to blindness, sensorineural hearing loss, diabetes and cardiomyopathy
	Bardet-Biedl	<i>BBS1 to BBS18</i> (mostly AR)			Cone-rod dystrophy, obesity, renal dysfunction, polydactyly, learning disabilities, hypogonadism and diabetes
	DNA damage repair disorders	<i>WRN</i> (AR) <i>BLM</i> (AR)			Scleroderma-like skin changes, cataracts, increased cancer risk, atherosclerosis and diabetes; Sun-sensitive, telangiectatic skin changes; increased cancer risk and diabetes
	Primordial dwarfism	<i>PCNT</i> (AR)			Microcephalic osteodysplastic primordial dwarfism and diabetes

References

1. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. *Diabetes Care*. 2011;34(8):1878-84.
2. Tattersall R. Maturity-onset diabetes of the young: a clinical history. *Diabet Med*. 1998;15(1):11-4.
3. Tattersall RB, Fajans SS. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes*. 1975;24(1):44-53.
4. Tattersall RB. Mild familial diabetes with dominant inheritance. *Q J Med*. 1974;43(170):339-57.
5. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. *Nat Clin Pract Endocrinol Metab*. 2008;4(4):200-13.
6. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med*. 2004;350(18):1838-49.
7. Bellanné-Chantelot C, Clauin S, Chauveau D, Collin P, Daumont M, et al. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes*. 2005;54(11):3126-32.
8. Støy J, Edghill EL, Flanagan SE, Ye H, Paz VP, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc Natl Acad Sci U S A*. 2007;104(38):15040-4.
9. Møller AM, Dalgaard LT, Pociot F, Nerup J, Hansen T, et al. Mutations in the hepatocyte nuclear factor-1alpha gene in Caucasian families originally classified as having Type I diabetes. *Diabetologia*. 1998;41(12):1528-31.
10. Lambert AP, Ellard S, Allen LI, Gallen IW, Gillespie KM, et al. Identifying hepatic nuclear factor 1alpha mutations in children and young adults with a clinical diagnosis of type 1 diabetes. *Diabetes Care*. 2003;26(2):333-7.
11. Awa WL, Schober E, Wiegand S, Herwig J, Meissner T, et al. Reclassification of diabetes type in pediatric patients initially classified as type 2 diabetes mellitus: 15 years follow-up using routine data from the German/Austrian DPV database. *Diabetes Res Clin Pract*. 2011.
12. Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, et al. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. *Genet Med*. 2018;20(6):583-90.
13. Fendler W, Borowiec M, Baranowska-Jazwiecka A, Szadkowska A, Skala-Zamorowska E, et al. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. *Diabetologia*. 2012;55(10):2631-5.
14. Irgens HU, Molnes J, Johansson BB, Ringdal M, Skrivarhaug T, et al. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. *Diabetologia*. 2013;56(7):1512-9.
15. Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. *J Clin Endocrinol Metab*. 2013;98(10):4055-62.
16. Johansson BB, Irgens HU, Molnes J, Sztromwasser P, Aukrust I, et al. Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. *Diabetologia*. 2017;60(4):625-35.
17. Delvecchio M, Mozzillo E, Salzano G, Iafusco D, Frontino G, et al. Monogenic Diabetes Accounts for 6.3% of Cases Referred to 15 Italian Pediatric Diabetes Centers During 2007 to 2012. *J Clin Endocrinol Metab*. 2017;102(6):1826-34.
18. Shepherd M, Shields B, Hammersley S, Hudson M, McDonald TJ, et al. Systematic

- Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. *Diabetes Care*. 2016;39(11):1879-88.
19. Bonnefond A, Philippe J, Durand E, Muller J, Saeed S, et al. Highly sensitive diagnosis of 43 monogenic forms of diabetes or obesity through one-step PCR-based enrichment in combination with next-generation sequencing. *Diabetes Care*. 2014;37(2):460-7.
 20. Ellard S, Lango Allen H, De Franco E, Flanagan SE, Hysenaj G, et al. Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. *Diabetologia*. 2013;56(9):1958-63.
 21. Gao R, Liu Y, Gjesing AP, Hollensted M, Wan X, et al. Evaluation of a target region capture sequencing platform using monogenic diabetes as a study-model. *BMC Genet*. 2014;15:13.
 22. Johansson S, Irgens H, Chudasama KK, Molnes J, Aerts J, et al. Exome sequencing and genetic testing for MODY. *PLoS ONE*. 2012;7(5):e38050.
 23. Alkorta-Aranburu G, Carmody D, Cheng YW, Nelakuditi V, Ma L, et al. Phenotypic heterogeneity in monogenic diabetes: the clinical and diagnostic utility of a gene panel-based next-generation sequencing approach. *Mol Genet Metab*. 2014;113(4):315-20.
 24. Greeley SA, John PM, Winn AN, Ornelas J, Lipton RB, et al. The cost-effectiveness of personalized genetic medicine: the case of genetic testing in neonatal diabetes. *Diabetes Care*. 2011;34(3):622-7.
 25. Naylor RN, John PM, Winn AN, Carmody D, Greeley SA, et al. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. *Diabetes Care*. 2014;37(1):202-9.
 26. De Franco E, Flanagan SE, Houghton JA, Lango Allen H, Mackay DJ, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet*. 2015;386(9997):957-63.
 27. Iafusco D, Stazi MA, Cotichini R, Cotellessa M, Martinucci ME, et al. Permanent diabetes mellitus in the first year of life. *Diabetologia*. 2002;45(6):798-804.
 28. Ellard S, Bellanne-Chantelot C, Hattersley AT. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. *Diabetologia*. 2008;51(4):546-53.
 29. Richards S, Aziz N, Bale S, Bick D, Das S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-24.
 30. Edghill EL, Dix RJ, Flanagan SE, Bingley PJ, Hattersley AT, et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. *Diabetes*. 2006;55(6):1895-8.
 31. Rubio-Cabezas O, Minton JA, Caswell R, Shield JP, Deiss D, et al. Clinical heterogeneity in patients with FOXP3 mutations presenting with permanent neonatal diabetes. *Diabetes Care*. 2009;32(1):111-6.
 32. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Allen HL, et al. Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. *Nature Genetics*. 2014;46(8):812-4.
 33. Johnson MB, De Franco E, Lango Allen H, Al Senani A, Elbarbary N, et al. Recessively Inherited LRBA Mutations Cause Autoimmunity Presenting as Neonatal Diabetes. *Diabetes*. 2017;66(8):2316-22.
 34. Rubio-Cabezas O, Flanagan SE, Damhuis A, Hattersley AT, Ellard S. KATP channel mutations in infants with permanent diabetes diagnosed after 6 months of life. *Pediatr Diabetes*. 2012;13(4):322-5.
 35. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, et al. Medical and

developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. *Pediatr Diabetes*. 2010;11(3):203-7.

36. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, et al. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. *Diabetes*. 2000;49(8):1359-66.

37. Gardner RJ, Mackay DJ, Mungall AJ, Polychronakos C, Siebert R, et al. An imprinted locus associated with transient neonatal diabetes mellitus. *Hum Mol Genet*. 2000;9(4):589-96.

38. Flanagan SE, Patch AM, Mackay DJ, Edghill EL, Gloyn AL, et al. Mutations in ATP-sensitive K⁺ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. *Diabetes*. 2007;56(7):1930-7.

39. Yorifuji T, Kurokawa K, Mamada M, Imai T, Kawai M, et al. Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: Phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. *Journal of Clinical Endocrinology & Metabolism*. 2004;89(6):2905-8.

40. Garin I, Edghill EL, Akerman I, Rubio-Cabezas O, Rica I, et al. Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. *Proc Natl Acad Sci U S A*. 2010;107(7):3105-10.

41. Russo L, Iafusco D, Brescianini S, Nocerino V, Bizzarri C, et al. Permanent diabetes during the first year of life: multiple gene screening in 54 patients. *Diabetologia*. 2011;54(7):1693-701.

42. Rubio-Cabezas O, Ellard S. Diabetes mellitus in neonates and infants: genetic heterogeneity, clinical approach to diagnosis, and therapeutic options. *Horm Res Paediatr*. 2013;80(3):137-46.

43. Mackay D, Bens S, Perez de Nanclares G, Siebert R, Temple IK. Clinical utility gene card for: Transient Neonatal Diabetes Mellitus, 6q24-related. *Eur J Hum Genet*. 2014;22(9).

44. Ma D, Shield JP, Dean W, Leclerc I, Knauf C, et al. Impaired glucose homeostasis in transgenic mice expressing the human transient neonatal diabetes mellitus locus, TNDM. *J Clin Invest*. 2004;114(3):339-48.

45. Temple IK, Shield JP. Transient neonatal diabetes, a disorder of imprinting. *J Med Genet*. 2002;39(12):872-5.

46. Mackay DJ, Boonen SE, Clayton-Smith J, Goodship J, Hahnemann JM, et al. A maternal hypomethylation syndrome presenting as transient neonatal diabetes mellitus. *Hum Genet*. 2006;120(2):262-9.

47. Mackay DJ, Callaway JL, Marks SM, White HE, Acerini CL, et al. Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in ZFP57. *Nat Genet*. 2008;40(8):949-51.

48. Docherty LE, Kabwama S, Lehmann A, Hawke E, Harrison L, et al. Clinical presentation of 6q24 transient neonatal diabetes mellitus (6q24 TNDM) and genotype-phenotype correlation in an international cohort of patients. *Diabetologia*. 2013;56(4):758-62.

49. Flanagan SE, Mackay DJ, Greeley SA, McDonald TJ, Mericq V, et al. Hypoglycaemia following diabetes remission in patients with 6q24 methylation defects: expanding the clinical phenotype. *Diabetologia*. 2013;56(1):218-21.

50. Kalaivanan P, Arya VB, Shah P, Datta V, Flanagan SE, et al. Chromosome 6q24 transient neonatal diabetes mellitus and protein sensitive hyperinsulinaemic hypoglycaemia. *J Pediatr Endocrinol Metab*. 2014;27(11-12):1065-9.

51. Shield JP, Temple IK, Sabin M, Mackay D, Robinson DO, et al. An assessment of pancreatic endocrine function and insulin sensitivity in patients with transient neonatal diabetes in remission. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(4):F341-3.

52. Busiah K, Drunat S, Vaivre-Douret L, Bonnefond A, Simon A, et al. Neuropsychological

dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study [corrected]. *Lancet Diabetes Endocrinol.* 2013;1(3):199-207.

53. Sovik O, Aagenaes O, Eide SA, Mackay D, Temple IK, et al. Familial occurrence of neonatal diabetes with duplications in chromosome 6q24: treatment with sulfonylurea and 40-yr follow-up. *Pediatr Diabetes.* 2012;13(2):155-62.

54. Yorifuji T, Hashimoto Y, Kawakita R, Hosokawa Y, Fujimaru R, et al. Relapsing 6q24-related transient neonatal diabetes mellitus successfully treated with a dipeptidyl peptidase-4 inhibitor: a case report. *Pediatr Diabetes.* 2014;15(8):606-10.

55. Carmody D, Beca FA, Bell CD, Hwang JL, Dickens JT, et al. Role of noninsulin therapies alone or in combination in chromosome 6q24-related transient neonatal diabetes: sulfonylurea improves but does not always normalize insulin secretion. *Diabetes Care.* 2015;38(6):e86-7.

56. Yorifuji T, Matsubara K, Sakakibara A, Hashimoto Y, Kawakita R, et al. Abnormalities in chromosome 6q24 as a cause of early-onset, non-obese, non-autoimmune diabetes mellitus without history of neonatal diabetes. *Diabet Med.* 2015;32(7):963-7.

57. McTaggart JS, Clark RH, Ashcroft FM. The role of the KATP channel in glucose homeostasis in health and disease: more than meets the islet. *J Physiol.* 2010;588(Pt 17):3201-9.

58. Ashcroft FM. ATP-sensitive potassium channelopathies: focus on insulin secretion. *J Clin Invest.* 2005;115(8):2047-58.

59. Babenko AP, Polak M, Cavé H, Busiah K, Czernichow P, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N Engl J Med.* 2006;355(5):456-66.

60. Ellard S, Flanagan SE, Girard CA, Patch AM, Harries LW, et al. Permanent neonatal diabetes caused by dominant, recessive, or compound heterozygous SUR1 mutations with opposite functional effects. *Am J Hum Genet.* 2007;81(2):375-82.

61. Flanagan SE, Edghill EL, Gloyn AL, Ellard S, Hattersley AT. Mutations in KCNJ11, which encodes Kir6.2, are a common cause of diabetes diagnosed in the first 6 months of life, with the phenotype determined by genotype. *Diabetologia.* 2006;49(6):1190-7.

62. Vaxillaire M, Populaire C, Busiah K, Cave H, Gloyn AL, et al. Kir6.2 mutations are a common cause of permanent neonatal diabetes in a large cohort of French patients. *Diabetes.* 2004;53(10):2719-22.

63. Flanagan SE, Dung VC, Houghton JAL, De Franco E, Ngoc CTB, et al. An ABCC8 Nonsense Mutation Causing Neonatal Diabetes Through Altered Transcript Expression. *J Clin Res Pediatr Endocrinol.* 2017;9(3):260-4.

64. Proks P, Arnold AL, Bruining J, Girard C, Flanagan SE, et al. A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. *Hum Mol Genet.* 2006;15(11):1793-800.

65. Letourneau LR, Carmody D, Wroblewski K, Denson AM, Sanyoura M, et al. Diabetes Presentation in Infancy: High Risk of Diabetic Ketoacidosis. *Diabetes Care.* 2017;40(10):e147-e8.

66. Gloyn AL, Diatloff-Zito C, Edghill EL, Bellanne-Chantelot C, Nivot S, et al. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. *Eur J Hum Genet.* 2006;14(7):824-30.

67. Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. *Diabetes.* 2005;54(9):2503-13.

68. Clark RH, McTaggart JS, Webster R, Mannikko R, Iberl M, et al. Muscle dysfunction caused by a KATP channel mutation in neonatal diabetes is neuronal in origin. *Science.* 2010;329(5990):458-61.

69. Beltrand J, Elie C, Busiah K, Fournier E, Boddaert N, et al. Sulfonylurea Therapy Benefits Neurological and Psychomotor Functions in Patients With Neonatal Diabetes Owing to Potassium

Channel Mutations. *Diabetes Care*. 2015;38(11):2033-41.

70. Carmody D, Pastore AN, Landmeier KA, Letourneau LR, Martin R, et al. Patients with KCNJ11-related diabetes frequently have neuropsychological impairments compared with sibling controls. *Diabet Med*. 2016;33(10):1380-6.
71. Bowman P, Broadbridge E, Knight BA, Pettit L, Flanagan SE, et al. Psychiatric morbidity in children with KCNJ11 neonatal diabetes. *Diabet Med*. 2016;33(10):1387-91.
72. Landmeier KA, Lanning M, Carmody D, Greeley SAW, Msall ME. ADHD, learning difficulties and sleep disturbances associated with KCNJ11-related neonatal diabetes. *Pediatr Diabetes*. 2017;18(7):518-23.
73. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*. 2006;355(5):467-77.
74. Rafiq M, Flanagan SE, Patch AM, Shields BM, Ellard S, et al. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. *Diabetes Care*. 2008;31(2):204-9.
75. Bowman P, Sulen A, Barbetti F, Beltrand J, Svalastoga P, et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. *Lancet Diabetes Endocrinol*. 2018.
76. Lanning MS, Carmody D, Szczerbinski L, Letourneau LR, Naylor RN, et al. Hypoglycemia in sulfonylurea-treated KCNJ11-neonatal diabetes: Mild-moderate symptomatic episodes occur infrequently but none involving unconsciousness or seizures. *Pediatr Diabetes*. 2018;19(3):393-7.
77. Sagen JV, Raeder H, Hathout E, Shehadeh N, Gudmundsson K, et al. Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: patient characteristics and initial response to sulfonylurea therapy. *Diabetes*. 2004;53(10):2713-8.
78. Greeley SA, Tucker SE, Naylor RN, Bell GI, Philipson LH. Neonatal diabetes mellitus: a model for personalized medicine. *Trends Endocrinol Metab*. 2010;21(8):464-72.
79. Thurber BW, Carmody D, Tadie EC, Pastore AN, Dickens JT, et al. Age at the time of sulfonylurea initiation influences treatment outcomes in KCNJ11-related neonatal diabetes. *Diabetologia*. 2015;58(7):1430-5.
80. Babiker T, Vedovato N, Patel K, Thomas N, Finn R, et al. Successful transfer to sulfonylureas in KCNJ11 neonatal diabetes is determined by the mutation and duration of diabetes. *Diabetologia*. 2016;59(6):1162-6.
81. Klupa T, Skupien J, Mirkiewicz-Sieradzka B, Gach A, Noczynska A, et al. Efficacy and safety of sulfonylurea use in permanent neonatal diabetes due to KCNJ11 gene mutations: 34-month median follow-up. *Diabetes Technology & Therapeutics*. 2010;12(5):387-91.
82. Codner E, Flanagan S, Ellard S, García H, Hattersley AT. High-dose glibenclamide can replace insulin therapy despite transitory diarrhea in early-onset diabetes caused by a novel R201L Kir6.2 mutation. *Diabetes Care*. 2005;28(3):758-9.
83. Kumaraguru J, Flanagan SE, Greeley SA, Nuboer R, Stoy J, et al. Tooth discoloration in patients with neonatal diabetes after transfer onto glibenclamide: a previously unreported side effect. *Diabetes Care*. 2009;32(8):1428-30.
84. Mlynarski W, Tarasov AI, Gach A, Girard CA, Pietrzak I, et al. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. *Nat Clin Pract Neurol*. 2007;3(11):640-5.
85. Fendler W, Pietrzak I, Brereton MF, Lahmann C, Gadzicki M, et al. Switching to sulphonylureas in children with iDEND syndrome caused by KCNJ11 mutations results in improved cerebellar perfusion. *Diabetes Care*. 2013;36(8):2311-6.
86. Lahmann C, Kramer HB, Ashcroft FM. Systemic Administration of Glibenclamide Fails to

Achieve Therapeutic Levels in the Brain and Cerebrospinal Fluid of Rodents. *PLoS One*. 2015;10(7):e0134476.

87. Battaglia D, Lin YW, Brogna C, Crino A, Grasso V, et al. Glyburide ameliorates motor coordination and glucose homeostasis in a child with diabetes associated with the KCNJ11/S225T, del226-232 mutation. *Pediatr Diabetes*. 2012;13(8):656-60.

88. Gurgel LC, Crispim F, Noffs MH, Belzunces E, Rahal MA, et al. Sulfonylurea treatment in permanent neonatal diabetes due to G53D mutation in the KCNJ11 gene: improvement in glycemic control and neurological function. *Diabetes Care*. 2007;30(11):e108.

89. Koster JC, Cadario F, Peruzzi C, Colombo C, Nichols CG, et al. The G53D mutation in Kir6.2 (KCNJ11) is associated with neonatal diabetes and motor dysfunction in adulthood that is improved with sulfonylurea therapy. *J Clin Endocrinol Metab*. 2008;93(3):1054-61.

90. Shah RP, Spruyt K, Kragie BC, Greeley SA, Msall ME. Visuomotor performance in KCNJ11-related neonatal diabetes is impaired in children with DEND-associated mutations and may be improved by early treatment with sulfonylureas. *Diabetes Care*. 2012;35(10):2086-8.

91. Edghill EL, Gloyn AL, Goriely A, Harries LW, Flanagan SE, et al. Origin of de novo KCNJ11 mutations and risk of neonatal diabetes for subsequent siblings. *J Clin Endocrinol Metab*. 2007;92(5):1773-7.

92. Edghill EL, Flanagan SE, Patch AM, Boustred C, Parrish A, et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. *Diabetes*. 2008;57(4):1034-42.

93. Polak M, Dechaume A, Cave H, Nimri R, Crosnier H, et al. Heterozygous Missense Mutations in the Insulin Gene Are Linked to Permanent Diabetes Appearing in the Neonatal Period or in Early Infancy: A Report From the French ND (Neonatal Diabetes) Study Group. *Diabetes*. 2008;57(4):1115-9.

94. Molven A, Ringdal M, Nordbo AM, Raeder H, Stoy J, et al. Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. *Diabetes*. 2008;57(4):1131-5.

95. Delépine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, et al. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat Genet*. 2000;25(4):406-9.

96. Senée V, Vatter KM, Delépine M, Rainbow LA, Haton C, et al. Wolcott-Rallison Syndrome: clinical, genetic, and functional study of EIF2AK3 mutations and suggestion of genetic heterogeneity. *Diabetes*. 2004;53(7):1876-83.

97. Habeb AM, Flanagan SE, Deeb A, Al-Alwan I, Alawneh H, et al. Permanent neonatal diabetes: different aetiology in Arabs compared to Europeans. *Arch Dis Child*. 2012;97(8):721-3.

98. Rubio-Cabezas O, Patch AM, Minton JA, Flanagan SE, Edghill EL, et al. Wolcott-Rallison syndrome is the most common genetic cause of permanent neonatal diabetes in consanguineous families. *Journal of Clinical Endocrinology & Metabolism*. 2009;94(11):4162-70.

99. Matschinsky FM. Glucokinase, glucose homeostasis, and diabetes mellitus. *Curr Diab Rep*. 2005;5(3):171-6.

100. Njolstad PR, Sagen JV, Bjorkhaug L, Odili S, Shehadeh N, et al. Permanent neonatal diabetes caused by glucokinase deficiency: inborn error of the glucose-insulin signaling pathway. *Diabetes*. 2003;52(11):2854-60.

101. Njolstad PR, Søvik O, Cuesta-Muñoz A, Bjørkhaug L, Massa O, et al. Neonatal diabetes mellitus due to complete glucokinase deficiency. *N Engl J Med*. 2001;344(21):1588-92.

102. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *NatGenet*. 2001;27(1):20-1.

103. Verbsky JW, Chatila TA. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked

- (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. *Curr Opin Pediatr.* 2013;25(6):708-14.
104. Bindl L, Torgerson T, Perroni L, Youssef N, Ochs HD, et al. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). *J Pediatr.* 2005;147(2):256-9.
105. Yong PL, Russo P, Sullivan KE. Use of sirolimus in IPEX and IPEX-like children. *J Clin Immunol.* 2008;28(5):581-7.
106. Rao A, Kamani N, Filipovich A, Lee SM, Davies SM, et al. Successful bone marrow transplantation for IPEX syndrome after reduced-intensity conditioning. *Blood.* 2007;109(1):383-5.
107. Weedon MN, Cebola I, Patch AM, Flanagan SE, De Franco E, et al. Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. *Nat Genet.* 2014;46(1):61-4.
108. Lango Allen H, Flanagan SE, Shaw-Smith C, De Franco E, Akerman I, et al. GATA6 haploinsufficiency causes pancreatic agenesis in humans. *Nat Genet.* 2012;44(1):20-2.
109. Habeb AM, Flanagan SE, Zulali MA, Abdullah MA, Pomahacova R, et al. Pharmacogenomics in diabetes: outcomes of thiamine therapy in TRMA syndrome. *Diabetologia.* 2018;61(5):1027-36.
110. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018;41(Suppl 1):S13-S27.
111. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, et al. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia.* 2010;53(12):2504-8.
112. Stanik J, Dusatkova P, Cinek O, Valentinova L, Huckova M, et al. De novo mutations of GCK, HNF1A and HNF4A may be more frequent in MODY than previously assumed. *Diabetologia.* 2014;57(3):480-4.
113. Lorini R, Klersy C, d'Annunzio G, Massa O, Minuto N, et al. Maturity-onset diabetes of the young in children with incidental hyperglycemia: a multicenter Italian study of 172 families. *Diabetes Care.* 2009;32(10):1864-6.
114. Prisco F, Iafusco D, Franzese A, Sulli N, Barbetti F. MODY 2 presenting as neonatal hyperglycaemia: a need to reshape the definition of "neonatal diabetes"? *Diabetologia.* 2000;43(10):1331-2.
115. Steele AM, Wensley KJ, Ellard S, Murphy R, Shepherd M, et al. Use of HbA1c in the identification of patients with hyperglycaemia caused by a glucokinase mutation: observational case control studies. *PLoS One.* 2013;8(6):e65326.
116. Stride A, Vaxillaire M, Tuomi T, Barbetti F, Njølstad PR, et al. The genetic abnormality in the beta cell determines the response to an oral glucose load. *Diabetologia.* 2002;45(3):427-35.
117. Chakera AJ, Spyer G, Vincent N, Ellard S, Hattersley AT, et al. The 0.1% of the population with glucokinase monogenic diabetes can be recognized by clinical characteristics in pregnancy: the Atlantic Diabetes in Pregnancy cohort. *Diabetes Care.* 2014;37(5):1230-6.
118. Rudland VL, Hinchcliffe M, Pinner J, Cole S, Mercorella B, et al. Identifying Glucokinase Monogenic Diabetes in a Multiethnic Gestational Diabetes Mellitus Cohort: New Pregnancy Screening Criteria and Utility of HbA1c. *Diabetes Care.* 2016;39(1):50-2.
119. Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, et al. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. *JAMA.* 2014;311(3):279-86.
120. Velho G, Blanché H, Vaxillaire M, Bellanné-Chantelot C, Pardini VC, et al. Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families. *Diabetologia.* 1997;40(2):217-24.
121. Stride A, Shields B, Gill-Carey O, Chakera AJ, Colclough K, et al. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations

does not alter glycaemia. *Diabetologia*. 2014;57(1):54-6.

122. Chakera AJ, Steele AM, Gloyn AL, Shepherd MH, Shields B, et al. Recognition and Management of Individuals With Hyperglycemia Because of a Heterozygous Glucokinase Mutation. *Diabetes Care*. 2015;38(7):1383-92.
123. Fendler W, Malachowska B, Baranowska-Jazwiecka A, Borowiec M, Wyka K, et al. Population-based estimates for double diabetes amongst people with glucokinase monogenic diabetes, GCK-MODY. *Diabet Med*. 2014;31(7):881-3.
124. Pearson ER, Pruhova S, Tack CJ, Johansen A, Castleden HA, et al. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. *Diabetologia*. 2005;48(5):878-85.
125. Ostoft SH, Bagger JI, Hansen T, Pedersen O, Holst JJ, et al. Incretin Effect and Glucagon Responses to Oral and Intravenous Glucose in Patients with Maturity Onset Diabetes of the Young - Type 2 and Type 3. *Diabetes*. 2014.
126. Isomaa B, Henricsson M, Lehto M, Forsblom C, Karanko S, et al. Chronic diabetic complications in patients with MODY3 diabetes. *Diabetologia*. 1998;41(4):467-73.
127. Steele AM, Shields BM, Shepherd M, Ellard S, Hattersley AT, et al. Increased all-cause and cardiovascular mortality in monogenic diabetes as a result of mutations in the HNF1A gene. *Diabet Med*. 2010;27(2):157-61.
128. Bellanne-Chantelot C, Carette C, Riveline JP, Valero R, Gautier JF, et al. The type and the position of HNF1A mutation modulate age at diagnosis of diabetes in patients with maturity-onset diabetes of the young (MODY)-3. *Diabetes*. 2008;57(2):503-8.
129. Harries LW, Ellard S, Stride A, Morgan NG, Hattersley AT. Isomers of the TCF1 gene encoding hepatocyte nuclear factor-1 alpha show differential expression in the pancreas and define the relationship between mutation position and clinical phenotype in monogenic diabetes. *Hum Mol Genet*. 2006;15(14):2216-24.
130. Stride A, Ellard S, Clark P, Shakespeare L, Salzman M, et al. Beta-cell dysfunction, insulin sensitivity, and glycosuria precede diabetes in hepatocyte nuclear factor-1alpha mutation carriers. *Diabetes Care*. 2005;28(7):1751-6.
131. Hamilton AJ, Bingham C, McDonald TJ, Cook PR, Caswell RC, et al. The HNF4A R76W mutation causes atypical dominant Fanconi syndrome in addition to a beta cell phenotype. *J Med Genet*. 2014;51(3):165-9.
132. Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, et al. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med*. 2007;4(4):e118.
133. Flanagan SE, Kapoor RR, Mali G, Cody D, Murphy N, et al. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. *Eur J Endocrinol*. 2010;162(5):987-92.
134. Kapoor RR, Locke J, Colclough K, Wales J, Conn JJ, et al. Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. *Diabetes*. 2008;57(6):1659-63.
135. Stanescu DE, Hughes N, Kaplan B, Stanley CA, De Leon DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. *J Clin Endocrinol Metab*. 2012;97(10):E2026-30.
136. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, et al. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet*. 2003;362(9392):1275-81.
137. Byrne MM, Sturis J, Menzel S, Yamagata K, Fajans SS, et al. Altered insulin secretory responses to glucose in diabetic and nondiabetic subjects with mutations in the diabetes susceptibility gene MODY3 on chromosome 12. *Diabetes*. 1996;45(11):1503-10.

138. Fajans SS, Brown MB. Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young. *Diabetes Care*. 1993;16(9):1254-61.
139. Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. *Diabet Med*. 2009;26(4):437-41.
140. Raile K, Schober E, Konrad K, Thon A, Grulich-Henn J, et al. Treatment of young patients with HNF1A mutations (HNF1A-MODY). *Diabet Med*. 2015;32(4):526-30.
141. Ostoft SH, Bagger JI, Hansen T, Pedersen O, Faber J, et al. Glucose-Lowering Effects and Low Risk of Hypoglycemia in Patients With Maturity-Onset Diabetes of the Young When Treated With a GLP-1 Receptor Agonist: A Double-Blind, Randomized, Crossover Trial. *Diabetes Care*. 2014.
142. Schmidt F, Kapellen TM, Wiegand S, Herbst A, Wolf J, et al. Diabetes mellitus in children and adolescents with genetic syndromes. *Exp Clin Endocrinol Diabetes*. 2012;120(10):579-85.
143. Farmer A, Ayme S, de Heredia ML, Maffei P, McCafferty S, et al. EURO-WABB: an EU rare diseases registry for Wolfram syndrome, Alstrom syndrome and Bardet-Biedl syndrome. *BMC Pediatr*. 2013;13:130.
144. Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet*. 1998;20(2):143-8.
145. Barrett TG, Bunday SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet*. 1995;346(8988):1458-63.
146. Marshall BA, Permutt MA, Paciorkowski AR, Hoekel J, Karzon R, et al. Phenotypic characteristics of early Wolfram syndrome. *Orphanet J Rare Dis*. 2013;8:64.
147. Karzon R, Narayanan A, Chen L, Lieu JEC, Hershey T. Longitudinal hearing loss in Wolfram syndrome. *Orphanet J Rare Dis*. 2018;13(1):102.
148. Bueno GE, Ruiz-Castaneda D, Martinez JR, Munoz MR, Alascio PC. Natural history and clinical characteristics of 50 patients with Wolfram syndrome. *Endocrine*. 2018.
149. de Heredia ML, Cleries R, Nunes V. Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype. *Genet Med*. 2013;15(7):497-506.
150. Zmyslowska A, Borowiec M, Fichna P, Iwaniszewska B, Majkowska L, et al. Delayed recognition of Wolfram syndrome frequently misdiagnosed as type 1 diabetes with early chronic complications. *Exp Clin Endocrinol Diabetes*. 2014;122(1):35-8.
151. Khanim F, Kirk J, Latif F, Barrett TG. WFS1/wolframin mutations, Wolfram syndrome, and associated diseases. *Hum Mutat*. 2001;17(5):357-67.
152. Amr S, Heisey C, Zhang M, Xia XJ, Shows KH, et al. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. *Am J Hum Genet*. 2007;81(4):673-83.
153. Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1beta. *Nephrol Dial Transplant*. 2004;19(11):2703-8.
154. Bellanné-Chantelot C, Clauin S, Chauveau D, Collin P, Daumont M, et al. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes*. 2005;54(11):3126-32.
155. Ulinski T, Lescure S, Beaufils S, Guignon V, Decramer S, et al. Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2) mutations in a pediatric cohort. *J Am Soc Nephrol*. 2006;17(2):497-503.
156. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta

- and their related phenotypes. *J Med Genet.* 2006;43(1):84-90.
157. Raile K, Klopocki E, Holder M, Wessel T, Galler A, et al. Expanded clinical spectrum in hepatocyte nuclear factor 1b-maturity-onset diabetes of the young. *J Clin Endocrinol Metab.* 2009;94(7):2658-64.
158. Edghill EL, Bingham C, Slingerland AS, Minton JA, Noordam C, et al. Hepatocyte nuclear factor-1 beta mutations cause neonatal diabetes and intrauterine growth retardation: support for a critical role of HNF-1beta in human pancreatic development. *Diabet Med.* 2006;23(12):1301-6.
159. Bellanné-Chantelot C, Chauveau D, Gautier JF, Dubois-Laforgue D, Clauin S, et al. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. *Ann Intern Med.* 2004;140(7):510-7.
160. Pearson ER, Badman MK, Lockwood CR, Clark PM, Ellard S, et al. Contrasting diabetes phenotypes associated with hepatocyte nuclear factor-1alpha and -1beta mutations. *Diabetes Care.* 2004;27(5):1102-7.
161. Tjora E, Wathle G, Erchinger F, Engjom T, Molven A, et al. Exocrine pancreatic function in hepatocyte nuclear factor 1beta-maturity-onset diabetes of the young (HNF1B-MODY) is only moderately reduced: compensatory hypersecretion from a hypoplastic pancreas. *Diabet Med.* 2013;30(8):946-55.
162. Haldorsen IS, Vesterhus M, Raeder H, Jensen DK, Sovik O, et al. Lack of pancreatic body and tail in HNF1B mutation carriers. *Diabet Med.* 2008;25(7):782-7.
163. Reinauer C, Meissner T, Roden M, Thon A, Holterhus PM, et al. Low prevalence of patients with mitochondrial disease in the German/Austrian DPV diabetes registry. *Eur J Pediatr.* 2016;175(5):613-22.
164. Maassen JA, LM TH, Van Essen E, Heine RJ, Nijpels G, et al. Mitochondrial diabetes: molecular mechanisms and clinical presentation. *Diabetes.* 2004;53 Suppl 1:S103-9.
165. Guillausseau PJ, Dubois-Laforgue D, Massin P, Laloi-Michelin M, Bellanne-Chantelot C, et al. Heterogeneity of diabetes phenotype in patients with 3243 bp mutation of mitochondrial DNA (Maternally Inherited Diabetes and Deafness or MIDD). *Diabetes Metab.* 2004;30(2):181-6.
166. Laloi-Michelin M, Meas T, Ambonville C, Bellanne-Chantelot C, Beaufile S, et al. The clinical variability of maternally inherited diabetes and deafness is associated with the degree of heteroplasmy in blood leukocytes. *J Clin Endocrinol Metab.* 2009;94(8):3025-30.
167. Goto Y, Nonaka I, Horai S. A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature.* 1990;348(6302):651-3.
168. Lalau JD. Lactic acidosis induced by metformin: incidence, management and prevention. *Drug Saf.* 2010;33(9):727-40.
169. Laloi-Michelin M, Virally M, Jardel C, Meas T, Ingster-Moati I, et al. Kearns Sayre syndrome: an unusual form of mitochondrial diabetes. *Diabetes Metab.* 2006;32(2):182-6.
170. Superti-Furga A, Schoenle E, Tuchschnid P, Caduff R, Sabato V, et al. Pearson bone marrow-pancreas syndrome with insulin-dependent diabetes, progressive renal tubulopathy, organic aciduria and elevated fetal haemoglobin caused by deletion and duplication of mitochondrial DNA. *Eur J Pediatr.* 1993;152(1):44-50.
171. Raeder H, Johansson S, Holm PI, Haldorsen IS, Mas E, et al. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat Genet.* 2006;38(1):54-62.
172. Raeder H, Haldorsen IS, Ersland L, Gruner R, Taxt T, et al. Pancreatic lipomatosis is a structural marker in nondiabetic children with mutations in carboxyl-ester lipase. *Diabetes.* 2007;56(2):444-9.
173. Raeder H, McAllister FE, Tjora E, Bhatt S, Haldorsen I, et al. Carboxyl-ester lipase maturity-onset diabetes of the young is associated with development of pancreatic cysts and upregulated MAPK signaling in secretin-stimulated duodenal fluid. *Diabetes.* 2014;63(1):259-69.

174. Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Le Marechal C, et al. The natural history of hereditary pancreatitis: a national series. *Gut*. 2009;58(1):97-103.
175. Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genetic syndromes of severe insulin resistance. *Endocr Rev*. 2011;32(4):498-514.
176. Parker VE, Semple RK. Genetics in endocrinology: genetic forms of severe insulin resistance: what endocrinologists should know. *Eur J Endocrinol*. 2013;169(4):R71-80.
177. Musso C, Cochran E, Moran SA, Skarulis MC, Oral EA, et al. Clinical course of genetic diseases of the insulin receptor (type A and Rabson-Mendenhall syndromes): a 30-year prospective. *Medicine (Baltimore)*. 2004;83(4):209-22.
178. Regan FM, Williams RM, McDonald A, Umpleby AM, Acerini CL, et al. Treatment with recombinant human insulin-like growth factor (rhIGF)-I/rhIGF binding protein-3 complex improves metabolic control in subjects with severe insulin resistance. *J Clin Endocrinol Metab*. 2010;95(5):2113-22.
179. Carmody D, Ladsaria SS, Buikema RK, Semple RK, Greeley SA. Successful rhIGF1 treatment for over 5 years in a patient with severe insulin resistance due to homozygous insulin receptor mutation. *Diabet Med*. 2016;33(3):e8-e12.
180. Garg A. Acquired and inherited lipodystrophies. *N Engl J Med*. 2004;350(12):1220-34.
181. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(12):4500-11.
182. Agarwal AK, Simha V, Oral EA, Moran SA, Gorden P, et al. Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. *J Clin Endocrinol Metab*. 2003;88(10):4840-7.
183. Weedon MN, Ellard S, Prindle MJ, Caswell R, Lango Allen H, et al. An in-frame deletion at the polymerase active site of *POLD1* causes a multisystem disorder with lipodystrophy. *Nat Genet*. 2013;45(8):947-50.
184. Chudasama KK, Winnay J, Johansson S, Claudi T, Konig R, et al. SHORT syndrome with partial lipodystrophy due to impaired phosphatidylinositol 3 kinase signaling. *Am J Hum Genet*. 2013;93(1):150-7.
185. Owen KR, Donohoe M, Ellard S, Hattersley AT. Response to treatment with rosiglitazone in familial partial lipodystrophy due to a mutation in the *LMNA* gene. *Diabet Med*. 2003;20(10):823-7.
186. Brown RJ, Oral EA, Cochran E, Araujo-Vilar D, Savage DB, et al. Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. *Endocrine*. 2018;60(3):479-89.
187. Simha V, Subramanyam L, Szczepaniak L, Quittner C, Adams-Huet B, et al. Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the Dunnigan variety. *J Clin Endocrinol Metab*. 2012;97(3):785-92.
188. Alstrom CH, Hallgren B, Nilsson LB, Asander H. Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from the Laurence-Moon-Bardet-Biedl syndrome: a clinical, endocrinological and genetic examination based on a large pedigree. *Acta Psychiatr Neurol Scand Suppl*. 1959;129:1-35.
189. Hearn T, Renforth GL, Spalluto C, Hanley NA, Piper K, et al. Mutation of *ALMS1*, a large gene with a tandem repeat encoding 47 amino acids, causes Alstrom syndrome. *Nat Genet*. 2002;31(1):79-83.
190. Mokashi A, Cummings EA. Presentation and course of diabetes in children and adolescents with Alstrom syndrome. *Pediatr Diabetes*. 2011;12(3 Pt 2):270-5.
191. Paisey RB, Geberhiwot T, Waterson M, Cramb R, Steeds R, et al. Modification of severe

- insulin resistant diabetes in response to lifestyle changes in Alstrom syndrome. *Eur J Med Genet.* 2014;57(2-3):71-5.
192. Tobin JL, Beales PL. Bardet-Biedl syndrome: beyond the cilium. *Pediatr Nephrol.* 2007;22(7):926-36.
193. Scheidecker S, Etard C, Pierce NW, Geoffroy V, Schaefer E, et al. Exome sequencing of Bardet-Biedl syndrome patient identifies a null mutation in the BBSome subunit BBIP1 (BBS18). *J Med Genet.* 2014;51(2):132-6.
194. Guo DF, Rahmouni K. Molecular basis of the obesity associated with Bardet-Biedl syndrome. *Trends Endocrinol Metab.* 2011;22(7):286-93.
195. Abu-Safieh L, Al-Anazi S, Al-Abdi L, Hashem M, Alkuraya H, et al. In search of triallelism in Bardet-Biedl syndrome. *Eur J Hum Genet.* 2012;20(4):420-7.
196. Katsanis N, Ansley SJ, Badano JL, Eichers ER, Lewis RA, et al. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. *Science.* 2001;293(5538):2256-9.
197. Stoffers DA, Ferrer J, Clarke WL, Habener JF. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. *Nat Genet.* 1997;17(2):138-9.
198. Sellick GS, Barker KT, Stolte-Dijkstra I, Fleischmann C, Coleman RJ, et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. *Nat Genet.* 2004;36(12):1301-5.
199. Smith SB, Qu HQ, Taleb N, Kishimoto NY, Scheel DW, et al. Rfx6 directs islet formation and insulin production in mice and humans. *Nature.* 2010;463(7282):775-80.
200. D'Amato E, Giacomelli F, Giannattasio A, D'Annunzio G, Bocciardi R, et al. Genetic investigation in an Italian child with an unusual association of atrial septal defect, attributable to a new familial GATA4 gene mutation, and neonatal diabetes due to pancreatic agenesis. *Diabet Med.* 2010;27(10):1195-200.
201. Senee V, Chelala C, Duchatelet S, Feng D, Blanc H, et al. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. *Nat Genet.* 2006;38(6):682-7.
202. Rubio-Cabezas O, Jensen JN, Hodgson MI, Codner E, Ellard S, et al. Permanent Neonatal Diabetes and Enteric Anendocrinosis Associated With Biallelic Mutations in NEUROG3. *Diabetes.* 2011;60(4):1349-53.
203. Rubio-Cabezas O, Minton JA, Kantor I, Williams D, Ellard S, et al. Homozygous mutations in NEUROD1 are responsible for a novel syndrome of permanent neonatal diabetes and neurological abnormalities. *Diabetes.* 2010;59(9):2326-31.
204. Solomon BD, Pineda-Alvarez DE, Balog JZ, Hadley D, Gropman AL, et al. Compound heterozygosity for mutations in PAX6 in a patient with complex brain anomaly, neonatal diabetes mellitus, and microphthalmia. *Am J Med Genet A.* 2009;149A(11):2543-6.
205. Sansbury FH, Flanagan SE, Houghton JA, Shuixian Shen FL, Al-Senani AM, et al. SLC2A2 mutations can cause neonatal diabetes, suggesting GLUT2 may have a role in human insulin secretion. *Diabetologia.* 2012;55(9):2381-5.
206. Shaw-Smith C, Flanagan SE, Patch AM, Grulich-Henn J, Habeb AM, et al. Recessive SLC19A2 mutations are a cause of neonatal diabetes mellitus in thiamine-responsive megaloblastic anaemia. *Pediatr Diabetes.* 2012;13(4):314-21.
207. Abdel-Salam GM, Schaffer AE, Zaki MS, Dixon-Salazar T, Mostafa IS, et al. A homozygous IER3IP1 mutation causes microcephaly with simplified gyral pattern, epilepsy, and permanent neonatal diabetes syndrome (MEDS). *Am J Med Genet A.* 2012;158A(11):2788-96.
208. Petrie JR, Chaturvedi N, Ford I, Brouwers MCGJ, Greenlaw N, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *The Lancet Diabetes & Endocrinology.* 2017;5(8):597-609.

209. De Franco E, Flanagan SE, Yagi T, Abreu D, Mahadevan J, et al. Dominant ER Stress-Inducing WFS1 Mutations Underlie a Genetic Syndrome of Neonatal/Infancy-Onset Diabetes, Congenital Sensorineural Deafness, and Congenital Cataracts. *Diabetes*. 2017;66(7):2044-53.
210. Yamagata K, Furuta H, Oda N, Kaisaki PJ, Menzel S, et al. Mutations in the hepatocyte nuclear factor-4alpha gene in maturity-onset diabetes of the young (MODY1). *Nature*. 1996;384(6608):458-60.
211. Vionnet N, Stoffel M, Takeda J, Yasuda K, Bell GI, et al. Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus. *Nature*. 1992;356(6371):721-2.
212. Yamagata K, Oda N, Kaisaki PJ, Menzel S, Furuta H, et al. Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3). *Nature*. 1996;384(6608):455-8.
213. Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet*. 1997;17(4):384-5.