

Current Insights into the Genetic Basis of Diabetes Mellitus in Children and Adolescents

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ABSTRACT

Diabetes mellitus (DM) is one of the most common chronic diseases in children and adolescents, and type 1 DM accounts for more than 95% of cases. Nevertheless, over the last years it has become apparent that not all cases of DM presenting in children have an autoimmune basis. In addition to type 2 DM, which continues to be an infrequent diagnosis among pediatric patients in most countries worldwide, several forms of monogenic DM may present during childhood and are responsible for the disease in 1-3% of patients. In these disorders, DM is usually associated with either specific clinical syndromes or a characteristic age of onset. Molecular diagnosis, increasingly available, improves both clinical management and quality of life, and is also important for genetic counselling. This review aims to provide physicians taking care of children with DM with some important clues in order to make an accurate diagnosis in these patients and understand its implication in clinical management.

KEY WORDS

type 1 diabetes mellitus, type 2 diabetes mellitus, monogenic diabetes, neonatal diabetes, polygenic diabetes, MODY, mitochondrial diabetes, *INS*,

KCNJ11, *ABCC8*, *GCK*, *ZAC*, *IPF1*, *PTF1A*, *HNF1B*, *GLIS3*, *SLC2A2*, *SLC19A2*, *EIF2AK3*, *FOXP3*, *HNF14A*, *NEUROD1*, *IPEX*, Fanconi-Bickel syndrome, Roger's syndrome, Wolfram syndrome, leprechaunism, lipodystrophies, Berardinelli-Seip syndrome, *LMNA*, *PPARG*, *AKT2*, Alström syndrome, Bardet-Biedl syndrome

INTRODUCTION

Diabetes mellitus (DM) is one of the most frequent chronic diseases in children and adolescents¹. It is not a single disease, but a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both².

Until recently, childhood DM has not been considered a diagnostic specialty, as patients were almost undoubtedly considered to have type 1 DM (DM1) and insulin was given from diagnosis. However, this assumption is no longer correct. Although DM1 accounts for the vast majority of cases of DM in children and adolescents (>95%), an increasing body of evidence demonstrates that several other types of DM can manifest during the first two decades of life³. This fact has important implications for clinical practice, as non-type 1 DM differs from DM1 not only in its cause, but also in its prognosis and associated conditions, and the cause of DM may even guide the most appropriate treatment. This has been proven to be true especially for certain subtypes of monogenic DM. The aim of this review is to give some practical clues for considering monogenic DM and genetic testing whenever facing a child with DM.

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POLYGENIC DIABETES

Genes play an important role in the development of DM, whichever type is considered. In most Western countries, DM1 accounts for more than 95% of childhood and adolescence diabetes.

Type

2 DM (DM2) is becoming more common and, although rare in unselected pediatric diabetic patients as a whole, it accounts for a significant proportion of youth-onset DM in certain at-risk populations⁴. The study of the genetics of polygenic DM, both DM1 and DM2, is fraught with difficulty because there are multiple predisposing polymorphisms, each having a small effect, while environmental factors also play a large role⁵.

Type 1 DM

DM1 results from selective destruction of the pancreatic insulin-producing β -cells, which occurs at a variable rate and becomes clinically symptomatic when approximately 90% of β -cells have been destroyed⁶. The β -cells are destroyed by an autoimmune response mediated by T cells that react specifically to one or more β -cell proteins. Serological markers of the autoimmune process, including islet cell (ICA), glutamic acid decarboxylase (GAD), islet antigen (IA)-2, or insulin (IAAs) autoantibodies, are present in 85-90% of affected children when fasting hyperglycemia is detected⁷; however, whether they participate in the pathogenic mechanism of the disease remains to be fully understood. When the clinical presentation is typical of DM1 (often associated with diabetic ketoacidosis⁸) but antibodies are absent, then the diabetes is classified as type 1b (idiopathic)⁹. The environmental triggers that initiate pancreatic β -cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms.

Familial aggregation of DM1 has been recognized for a long time, and ~10-13% of newly diagnosed children have a first-degree relative affected with DM1, this proportion being higher for siblings of affected patients than for offspring or

parents. The risk of DM to an identical twin of a patient with DM1 is about 36% and for a sibling the risk is approximately 4% by the age of 20 years and 9.6% by the age of 60 years, compared with 0.5% for the general population. The younger the proband is at diagnosis, the higher the risk for siblings. DM1 is two to three times more common in the offspring of diabetic men (3.6-8.5%) compared with diabetic women (1.3-3.6%)¹⁰.

Despite this familial clustering, there is no recognizable pattern of inheritance of the disease. Instead, association studies exploiting unbiased genome-wide analyses have identified over 20 regions in the human genome that are linked to DM1, but most make only a minor contribution overall to the genetic susceptibility to this disease¹¹⁻¹³. The most significant susceptibility locus (*IDDM1* locus) is the HLA class II region in the major histocompatibility complex on chromosome 6p21.3, as allelic variation within this locus contributes about 50% of the inherited risk for DM1. The disease susceptibility conferred by HLA represents the combined effect of several genes within the region, *DRB1* and *DQB1* genes being the major determinants of HLA-encoded susceptibility to DM1. Whereas several HLA genotypes confer increased risk, other genotypes confer protection. In Caucasians, DM1 is strongly associated with HLA DR3-DQ2 and DR4-DQ8 haplotypes, and recent studies from different European countries have confirmed that the HLA DR3-DQ2/DR4-DQ8 genotype is associated with the highest diabetes risk. This genotype is found in 20-30% of patients with DM1 and in almost 50% of patients diagnosed in early childhood. In contrast, genotypes containing the HLA DQ6 haplotype confer dominant protection from DM1. Several other disease susceptibility loci have been clearly demonstrated based on their direct effect on risk. However, a large proportion of DM1 clustering remains unexplained¹⁴.

More than half of individuals with DM1 are diagnosed before the age of 15 years. A well-documented rise in the incidence has been noted in many countries (approximately 3% per year)¹⁵, and in some reports, there has been a disproportionately greater increase in those under 5 years old. As a rule of thumb, the earlier the onset of the disease,

the stronger the HLA-defined genetic susceptibility and the more frequently is an autoantibody response detected¹⁶. Nevertheless, among those patients with DM1 diagnosed during childhood, less than 5% present clinically in the first 2 years after birth. Moreover, because months or even years can elapse between the beginning of the auto-immune response and the clinical appearance of DM1, the onset of DM very early in life might not be consistent with the time required for an auto-immune response to result in overt DM, even if the autoimmune disease begins in the fetal period^{17,18}. Thus, clinical presentation of DM1 is extremely rare in infants, especially within the first 6 months of life. Children diagnosed after the sixth month of life have an HLA-DQA1 and DQB1 genotype distribution similar to older classical DM1 patients, whereas children with 'early onset' DM are similar to control subjects^{19,20}. These data are even more relevant if we consider that patients with DM1 diagnosed in childhood are more likely than adults to carry HLA alleles associated with disease susceptibility and, in addition, in very young children DM appears to be associated with a higher-risk genotype than in older children. Individuals diagnosed before 6 months of age are therefore unlikely to have DM1. However, it is difficult to be certain of an absolute cut-off at 6 months. The fact that the prevalence of high-risk HLA is slightly lower in those diagnosed between 6 and 12 months of age compared with those between 12 and 24 months of age indicates that there may be a few patients with non-autoimmune DM in the 6-12 month age range²⁰. There is not a role for HLA class II genotyping in the classification of DM1 on an individual basis. Although the absence of a high-risk HLA genotype makes DM1 unlikely, the presence of high-risk HLA does not exclude non-autoimmune DM¹⁰.

Type 2 DM

DM2 is often considered a polygenic disorder with multiple genes located on different chromosomes being associated with this condition. This is further complicated by numerous environmental factors that also contribute to the clinical manifestation of the disorder in genetically predisposed persons²¹. Once considered almost

restricted to adults, the incidence of DM2 is increasing among pediatric patients⁴. The rapid increase in the population prevalence of DM2 in youth can only be explained by changes in lifestyle, as it parallels the increasing incidence of childhood obesity worldwide. However, even in sedentary Western culture, only a small minority of obese children develops DM2. Genetic factors are important in determining the children who become obese and also the obese children who develop DM2⁵. Support for the role of genetic factors comes from epidemiological evidence that DM2 in youth is most common in individuals from racial groups with a high prevalence of DM and in individuals with a strong family history. *TCF7L2* has recently been discovered as the gene with the greatest impact on the risk of DM2 at least in European populations²²⁻²⁷. However, systematic population screening for DM2 cannot be justified in most countries because of the low prevalence. Nevertheless, targeted screening is recommended if youths are overweight and have any two risk factors listed in Table 1, starting at 10 years or at the onset of puberty, whichever is earlier, and every 2 years thereafter²⁸.

MONOGENIC DIABETES

Monogenic DM results from the presence of one or more mutations in a single gene. It may be dominantly or recessively inherited or may have arisen *de novo* and, hence, familial history might be lacking.

Almost all cases of monogenic DM in children and adolescents result from mutations in genes causing β -cell loss or β -cell dysfunction and hence affect insulin synthesis, packaging, glucose sensing or insulin secretion, although DM can rarely occur from mutations resulting in very severe insulin resistance²⁹. Thus, monogenic DM pathophysiologically mimics polygenic DM, i.e. most cases are due to an absolute insulin deficiency.

Only a minority of cases of DM (no more than 1-3%) is caused by single gene defects. However, it is important to correctly diagnose monogenic DM as it not only predicts the clinical course of the patient and explains other associated clinical features, but can also guide the physician in pre-

scribing the most appropriate treatment. In addition, making a specific diagnosis will have important implications for other family members and allow appropriate genetic counselling³⁰.

tab 1

4. Absent pancreatic islet autoantibodies, especially if measured at diagnosis;
5. Non-high risk HLA haplotype.

The majority of patients with genetically proven monogenic DM are initially incorrectly diagnosed as having DM1 or DM2 (Table 2). Thus, pediatric endocrinologists should be aware of a number of features that might suggest a possible diagnosis of monogenic DM. None of them are absolute, and thus they should be considered together, rather than in isolation²⁹.

For DM1, these characteristics are:

1. Diagnosis of DM before 6 months of age;
2. Family history of DM with a parent affected;
3. Evidence of endogenous insulin production outside the 'honeymoon' phase (after 3 years of DM), with detectable C-peptide (>200 nmol/l) when glucose level is >8 mmol/l;

Features in children initially thought to have DM2 that might suggest a monogenic subtype of DM are:

1. Not markedly obese or diabetic family members who are of normal weight;
2. Absence of acanthosis nigricans;
3. Ethnic background with a low prevalence of DM2, e.g., European Caucasian;
4. No evidence of insulin resistance with fasting C-peptide within the normal range.

In addition to having clinical features that are unusual for DM1 and DM2, a patient who is to be diagnosed with monogenic DM should also have the features of a specific genetic subtype of mono-

genic DM. There are four main categories to be considered:

1. Neonatal DM and DM diagnosed in early infancy;

tab 2 &3

2. Familial DM with autosomal dominant inheritance (at least one parent affected);
3. Familial, mild fasting hyperglycemia;
4. DM associated with extrapancreatic features.

NEONATAL DIABETES AND DIABETES MELLITUS DIAGNOSED IN EARLY INFANCY

As previously stated, all cases of DM diagnosed before 6 months of age are likely to be one of the monogenic forms of neonatal DM and not classical DM1. Many of these patients are born small for gestational age, which reflects a prenatal lack of insulin and its important growth-promoting function during intrauterine development³¹.

The DM resolves in approximately half of the patients with neonatal DM (transient neonatal diabetes [TNDM]), most often during the first year of life. The remaining 50% of patients continue to need treatment for life (permanent neonatal diabetes [PNDM])³². At the time of diagnosis, it is not possible to predict whether the DM in an infant will be transient or permanent, so genetic studies should be carried out following the most likely molecular diagnosis in terms of frequency.

Transient neonatal diabetes

A genetic diagnosis is now possible for most patients diagnosed with TNDM³³. The majority of cases (~70%) are linked to *imprinting* abnormalities on chromosome 6q24. Activating mutations in one of the genes encoding the ATP-sensitive potassium channel of the β -cell membrane (*KCNJ11* or *ABCC8*) account for most of the remaining cases (~25%) (Table 3), although they are predominantly associated with PNDM (see below).

TNDM due to disordered imprinting

This change is the single most frequent genetic cause of neonatal DM³⁴. To date, three different molecular mechanisms have been shown to be involved: paternal uniparental disomy of chromosome 6 (either complete³⁵ or partial³⁶, accounts for 50% of sporadic TNDM cases), unbalanced paternal duplication of 6q24³⁷ (found in most familial

cases) and abnormal methylation of the maternal copy of chromosome 6³⁸ (found in some sporadic cases). In all cases, the common result is the bi-allelic expression of one or more genes located in the 6q24 region, rather than the normal paternally-restricted monoallelic expression due to methylation and inactivation of the copy inherited from the mother. There are no phenotypic differences among the three subgroups of patients³⁹. It has recently been found that the overexpression of some genes located in this region in a mouse model reproduces the clinical phenotype of patients quite accurately and leads, in turn, to a decrease in the expression of some transcription factors required for embryonic development of pancreatic islets and mature β -cell functioning (Pdx1, Ngn3 and Pax6)⁴⁰. The strongest candidate gene appears to be *ZAC* (Z finger protein that regulates Apoptosis and Cell cycle arrest)⁴¹. It encodes a transcription factor that is involved in the regulation of cell cycle and apoptosis, as well as the expression of the type 1 receptor peptide PACAP (Pituitary Adenylate Cyclase Activating Polypeptide), a potent insulin secretagogue that stimulates proliferation of β -cells. Thus, overexpression of *ZAC* might alter pancreatic functioning by one or more of the following mechanisms: a) altering the proliferation or the programmed death of pancreatic β -cells, b) altering the transcriptional regulation of the endocrine pancreas, or c) affecting gene expression in mature β -cells, thereby altering the secretion of insulin in response to glucose or other stimuli⁴⁰.

Imprinting abnormalities on chromosome 6q24 originate four distinct clinical phases³⁹:

- a. *Intrauterine phase*. Fetal insulin deficiency during pregnancy leads to intrauterine growth retardation. Thus, affected children are born small for dates (mean birth weight 2,000 g).
- b. *Neonatal phase*. Patients develop hyperglycemia and osmotic dehydration very early, usually without accompanying ketosis, and TNDM is diagnosed within the first week of life (range 1-81 days). Despite the severe insulin deficiency at birth, 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 the patients have macroglossia, and occasionally an umbilical hernia is present.

These findings also appear in children with Beckwith-Wiedemann syndrome, a disease also caused by an alteration of imprinting at a different locus (11p15.5), and might present associated with TNDM as part of a more general methylation defect involving several chromosomes⁴².

c. *Remission phase*. Patients remain asymptomatic and have a normal glucose tolerance, but may develop hyperglycemia during intercurrent illnesses⁴³.

d. *Relapse phase*. Diabetes relapse rate is at least 50-60%, usually during puberty, although recurrences have been described from 4 years of age. Relapse resembles early-onset DM2 and is characterized by a loss of first-phase insulin secretion in response to hyperglycemia. Insulin treatment in these cases is not a must, and if needed, required doses tend to be lower than those given in DM1. Of note, glucagon-induced insulin secretion remains intact, suggesting that the signaling pathway through G proteins and cyclic AMP could provide a potential therapeutic target (i.e. GLP-1 analogues)⁴⁴.

The phases described above do not present irretrievably in every patient. In spite of showing the same genetic abnormalities, some relatives of children with TNDM develop DM2 or gestational DM during adulthood without any evidence of neonatal DM, suggesting that there may be other genetic or epigenetic factors influencing the clinical expression of imprinting defects³⁴. On the other hand, there is no evidence indicating that the TNDM region at 6q24 contributes significantly to the most frequent forms of DM in the general population, such as DM2 or MODY³⁹.

Genetic counseling of families with TNDM depends on the genetic etiology. Cases with uniparental disomy of chromosome 6 are sporadic and, therefore, have low recurrence risk in siblings and offspring. In cases of familial paternal duplications of the 6q24 region, males have a 50% chance of transmitting TNDM to their children. If females pass on this duplication, their children will not be affected, but the sons may pass on the risk of TNDM to their own children³⁰.

Permanent neonatal diabetes

In contrast to TNDM, the genetic basis of PNDM can be identified in around 60% of probands⁴⁵. Many of them will have isolated PNDM, some will develop a number of extrapancreatic features, and in approximately 10% of cases DM will be a consequence of pancreatic aplasia/hypoplasia.

1. Neonatal diabetes due to activating mutations in the ATP-sensitive potassium channel

The 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*, respectively⁴⁶. These channels regulate insulin secretion by linking intracellular metabolic state to β -cell membrane electrical activity and can be found in different cell types, including endocrine cells, neurons and muscle cells⁴⁷. Any increase in intracellular metabolic activity induces an increase in the ATP/ADP ratio within the cell which makes the K_{ATP} channels close. This leads to cell membrane depolarization that ultimately triggers the secretion of insulin⁴⁸. Among individuals with PNDM, mutations in *KCNJ11* or *ABCC8* are found in nearly half of the patients (~30% *KCNJ11*, ~10% *ABCC8*)⁴⁶. These mutations mostly reduce the response of the channel to ATP, which prevents channel closure and consequent insulin secretion.

The specific mutation determines the phenotype⁴⁸, and there is a striking correlation with the functional severity of the mutation, although there are a few exceptions⁴⁹. The majority of patients with Kir6.2 neonatal diabetes (i.e. neonatal diabetes caused by *KCNJ11* mutations) have isolated DM, and most have PNDM rather than TNDM (~10%). The DM typically presents from birth to 26 weeks of age (mean 5 weeks), usually with marked hyperglycemia and ketoacidosis (~30%)⁴⁸. Low birth weight (mean 2,500 g) is common although less severe than among patients with 6q24 imprinting abnormalities. Due to the expression of the K_{ATP} channel in both neurons and muscles, around 20% of probands with PNDM present with associated neurological features. They occasionally constitute a severe syndrome of developmental delay,

epilepsy and neonatal diabetes (DEND)^{50,51}. However, an intermediate DEND syndrome, which is characterized by DM and less severe developmental delay without epilepsy, is more common. SUR1 neonatal diabetes has a similar phenotype, but TNDM is more common than PNDM, and neurological features are not as common and usually include speech delay and feeding behavior abnormalities^{52,53}. As in patients with 6q24 imprinting abnormalities, K_{ATP}-associated TNDM can relapse later in life⁵²⁻⁵⁴.

It is important to identify patients with activating K_{ATP} channel mutations because despite being insulin dependent, oral sulfonylureas provide the most effective therapy.^{55,56} They bind the SUR subunit and close the channel in an ATP-independent manner.

Approximately 90% of patients with Kir6.2 DM and 85% of those with SUR1 DM can transfer from insulin to sulfonylurea tablets and achieve improved glycemic control, without a higher risk of developing hypoglycemia. However, the doses required are considerably higher than those used in DM2⁵⁵ (somewhat lower in patients with *ABCC8* activating mutations than in those with *KCNJ11* mutations)⁵⁶, and may cause transient diarrhea⁵⁷. As glibenclamide binds non-specifically to SUR subunits found in K_{ATP} channels in nerve, muscle and brain, as well as in β -cells, it can partially improve some of the associated neurological symptoms^{58,59}.

Kir6.2 DM is associated with activating heterozygous *KCNJ11* mutations. Patients are usually born to parents who do not have DM, as around 90% of mutations arise *de novo*. Familial cases show autosomal dominant inheritance. Thus, the risk of neonatal DM for each future child of an affected person is 50%. Similarly, most children with SUR1 DM lack a family history of DM. The majority of sporadic cases also result from *de novo* heterozygous mutations, and affected individuals also have 50% chance of passing on the mutation to their children. However, around 40% of patients with PNDM as a result of *ABCC8* mutations show recessive inheritance⁵³. In these cases, the risk of neonatal DM for each future sibling of the patients is 25%, but the affected child is at very low risk of having affected offspring. Nonetheless, unaffected

parents of a child with a *de novo* mutation should be counselled that the recurrence risk of a second child being affected is not negligible because germline mosaicism (in which mutations may be present in the gonads but not detectable in blood) has been reported in several families^{60,61}.

2. PNDM due to mutations in the insulin gene

Heterozygous mutations in the insulin gene (*INS*) have been identified and could account for 10-13% of cases of PNDM^{45,62-64}. Most mutations are located within the A or B chains of insulin and are predicted to interfere with the formation of disulfide bridges between cysteine residues, either by replacing a cysteine residue or introducing an additional cysteine residue into the insulin molecule. Thus, *INS* mutations result in a misfolded pro-insulin molecule that is trapped and accumulated in the endoplasmic reticulum, leading to induction of the endoplasmic reticulum stress response, inhibition of protein synthesis and ultimately β -cell death⁶⁵.

Patients with PNDM and an *INS* mutation have PNDM without any extrapancreatic features except low birth weight, which is a feature of all subtypes of neonatal DM. Moreover, no difference in birth weight has been observed between patients with *INS* mutations and those with activating *KCNJ11* or *ABCC8* mutations (Table 4). Although patients with *INS* gene mutations are diagnosed later, the ranges overlap and hence patients diagnosed within the first 6 months with permanent DM require molecular genetic testing to confirm the genetic subtype. As this type of monogenic DM involves the progressive death of β -cells, insulin is the only treatment available for these patients.

The majority of patients with an *INS* mutation are sporadic cases that result from *de novo* mutations. Only ~20% of cases run in families showing an autosomal dominant inheritance pattern⁶². The risk of passing on the disease to their children for affected individuals is thus 50%.

Interestingly, both *INS* and *KCNJ11* mutations are a rare cause of permanent DM diagnosed between 6 and 12 months. This should be taken into account when facing diabetic infants, especially if they do not have either pancreatic auto-antibodies or a high-risk HLA haplotype for DM1.

tab 4

3. PNDM due to mutations in the glucokinase gene

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 glycemia⁶⁶.

Heterozygous *GCK* gene mutations produce familial, mild, non-progressive hyperglycemia (see below). However, complete glucokinase deficiency associated with mutations in both alleles (homozygous or compound heterozygous) prevents the β -cells from secreting insulin in response to hyperglycemia⁶⁷⁻⁷⁰. This mechanism underlies not more than 4-5% of cases of PNDM³⁰. Hyperglycemia can be detected on the first day of life and is accompanied by severe intrauterine growth retardation (mean birth weight 1,700 g). Patients do not have any relevant extrapancreatic features and require treatment with insulin for life.

This diagnosis should be strongly considered in consanguineous families, especially if both parents have mild hyperglycemia. As it is usually asymptomatic, testing fasting blood glucose in the parents of every infant with neonatal DM should be a must, even if there is no family history of known DM. This type of PNDM is inherited in a recessive manner, so the recurrence risk among the future siblings of a given patient is 25%.

4. Other subtypes of PNDM

The remaining known genetic causes of neonatal DM are uncommon (Table 5). Associated clinical data and knowledge of consanguinity can be very helpful when deciding whether to test for other genetic subtypes.

- Pancreatic aplasia or hypoplasia accounts for around 5-10% of PNDM cases. Most of these patients remain genetically undiagnosed, although a number of genes have been identified in a few patients:
 - Complete deficiency of the transcription factor IPF1 secondary to homozygous or compound heterozygous mutations in the *IPF1* gene has been described in two patients with pancreatic agenesis to date^{71,72}. IPF1 is essential for embryonic development of the pancreas, as it regulates the differentiation process from mid-gut endodermic stem cells. In adults, it also participates in *INS* transcription. Thus, heterozygous mutations of *IPF1* are responsible for rare cases of familial early-onset DM⁷³. Several polymorphic variants of the gene confer a higher risk for developing DM2 as well⁷⁴.
 - Homozygous mutations in *PTF1A*, encoding the pancreas transcription factor 1- α , have been identified in several patients with pancreatic and cerebellar hypoplasia/agenesis from two consanguineous families^{75,76}.

All of them died during infancy due to central respiratory failure.

- *GLIS3* is a widely expressed transcriptional regulator that has recently been shown to be involved in the production of a complex syndrome including neonatal DM, congenital hypothyroidism and dysmorphic features^{77,78}. Some patients also presented with congenital glaucoma, hepatic fibrosis and renal cysts. To date, homozygous mutations in the *GLIS3* gene have

been identified in four probands from three unrelated consanguineous families.

- IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome is a multisystemic disorder that presents in hemizygous males with a mutation in the *FOXP3* gene⁷⁹. The protein encoded by this gene is necessary for the proper development and function of regulatory T cells⁸⁰. Its lack is associated with the presence of numerous early-

onset autoimmune diseases (enteropathy, DM, eczematous dermatitis, hypothyroidism, cytopenias, etc.) that leads to the patient's death usually within the first years of life. Remarkably, antibodies against β -cell antigens can be found, representing an important difference from other causes of PNDM. Immunosuppressive drugs and bone marrow transplantation are both included in the treatment regimen⁸¹. Heterozygous carrier females remain asymptomatic.

The remaining subtypes of DM with associated extrapancreatic features, although having been described in a number of patients with PNDM, mainly produce DM beyond the first 6 months of life, and hence are described below.

FAMILIAL DIABETES WITH AUTOSOMAL DOMINANT INHERITANCE

The confusing term MODY (maturity-onset diabetes of the young) originates from the time when the terms juvenile-onset and maturity-onset were used to distinguish between DM1 (insulin-dependent) and DM2 (non-insulin-dependent). MODY was used to describe a subgroup of autosomal dominantly inherited DM that was initially non-insulin-dependent despite having a young age of onset (at least one family member diagnosed before 25 years of age)⁸². The different genetic subtypes differ in age of onset, pattern of hyperglycemia, response to treatment and associated extrapancreatic manifestations, which suggests that it is inappropriate to place them into a single category. Since the classification of DM was revised in 1998 to reflect etiology⁸³, the term MODY is now obsolete and the correct monogenic names of the different forms of young-onset DM should be used when possible.

Those patients in whom DM (not just mild hyperglycemia) is diagnosed before age 25 years and do not fit the phenotypes of either DM1 or DM2, and who also have a strong family history of DM, need to be evaluated for mutations in a number of β -cell transcription factors. Patients with these mutations have normal glucose levels at birth and progressive deterioration in glucose tolerance. As a consequence of their increasing

hyperglycemia they are at high risk of diabetic complications. In the early stages of DM, fasting glucose remains relatively normal initially, but increases greatly following meals or an oral glucose tolerance test (OGTT) (typically >4.5 mmol/l or >80 mg/dl)⁸⁴.

HNF1A diabetes (former MODY3)

This is by far the commonest monogenic form of transcription factor DM (estimated population frequency of approximately 0.02-0.04%), although most cases are not diagnosed³⁰. Thus, it is the first gene that should be tested whenever facing a patient with familial, dominantly inherited early-onset DM. An individual with *HNF1A* DM has 50% chance of passing on the mutation to each child.

Patients with heterozygous *HNF1A* mutations typically present in adolescence or early adult life with symptomatic DM. Initially, despite having normal fasting plasma glucose, they show marked postprandial hyperglycemia. However, progressive β -cell failure results in increasing hyperglycemia throughout life. The frequency of microvascular complications in patients with *HNF1A* DM is similar to that in patients with DM1 and DM2, and is related to poor glycemic control⁸⁵. Nonetheless, the frequency of coronary heart disease appears to be greater in patients with *HNF1A* DM, despite increased HDL-cholesterol levels that do not, however, seem to be cardioprotective⁸⁶.

HNF1A mutations have a high penetrance, with 63% of carriers developing DM by 25 years of age, 79% by 35 years and 96% by 55 years³⁰. The age at diagnosis is determined in part by the location of the mutation: patients with mutations in the terminal exons (8-10) are diagnosed on average 8 years later than those with mutations in exons 1-6^{87,88}. Intrauterine exposure to maternal DM, when the mutation is inherited from the mother, reduces the age of onset of this type of DM in the offspring by approximately 12 years^{89,90}.

Postprandial glycosuria is a key feature of *HNF1A* mutation carriers before they develop DM and is due to defective renal tubular transport of glucose⁹¹. A positive urine test for glycosuria after a large unrefined carbohydrate meal could, therefore, suggest the need for a formal OGTT and

genetic testing in young children from families with an *HNF1A* mutation.

The importance of diagnosing patients who have *HNF1A* DM is that this type of DM is very sensitive to sulfonylurea therapy⁹², at least in part as a consequence of decreased liver uptake of the drug⁹³. Glycemic control by sulfonylureas is often better than that achieved by insulin, especially in children and young adults. The initial dose of sulfonylurea 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. If there is hypoglycemia despite dose titration of a once- or twice-daily sulfonylurea preparation such as gliclazide, a slow release preparation or meal time doses with a short-acting agent like nateglinide may be considered⁹⁴.

***HNF4A* diabetes (former MODY1)**

DM due to mutations of the *HNF4A* gene is considerably less common than *HNF1A* DM (it affects 20-30% of patients thought to have transcription factor DM who do not have a mutation in *HNF1A*), but has similar characteristics⁹⁵. Patients with heterozygous *HNF4A* mutations also have progressive β -cell dysfunction and glucose intolerance beginning around puberty, and long-term treatment with low-dose sulfonylureas seems effective. However, a number of differences are also evident: there is no low renal threshold for glucose, patients have reduced levels of HDL-cholesterol and tend to have increased levels of LDL-cholesterol, and affected newborns show increased birth weight (by ~800 g) and macrosomia⁹⁶. Interestingly, either transient or persistent neonatal hypoglycemia may precede the DM in *HNF4A* mutation carriers^{96,97}, but the mechanism underlying the biphasic pattern of hyperinsulinism *in utero* followed by DM in later life is unknown. Genetic counselling is similar to that for individuals with *HNF1A* mutations.

Other subtypes

Mutations in the transcription factor genes *IPF1* (former MODY4)⁷³ and *NEUROD1* (former

MODY6)⁹⁸⁻¹⁰¹ are extremely rare, but the phenotype of the patients resembles that found in individuals with mutations in the transcription factor *HNF1A*. Three mutations in the *INS* gene have been identified in families with MODY^{45,64}, two mutations in the transcription factor gene *PAX4* in Thai families¹⁰², and a further *ISL1* mutation in a Japanese family¹⁰³. However, these diagnoses are so unusual they do not need to be tested for in children with DM except in a research setting.

Two families with DM and exocrine pancreatic dysfunction have been found who have mutations in the gene encoding the enzyme carboxyl ester lipase (*CEL*)^{104,105}, which is not expressed in β -cells but in pancreatic acinar cells. Moreover, there are a number of other monogenic disorders that primarily affect the exocrine pancreas and may eventually produce DM sooner or later, including those responsible for cystic fibrosis (*CFTR*)¹⁰⁶ and hereditary pancreatitis (*PRSSI* and *SPINK1*)¹⁰⁷. Thus, the proposed name of MODY7 for DM secondary to *CEL* mutations remains controversial.

Depending on the country, a genetic diagnosis cannot be made in between 11% (UK)¹⁰⁸ and >80% (Korea)¹⁰⁹ of families with autosomal dominant β -cell disease, presumably because of the presence of as yet undetermined gene mutations.

FAMILIAL, MILD FASTING HYPERGLYCEMIA

The finding of raised fasting blood glucose in the range of 5.5-8.0 mmol/l (100-145 mg/dl) is unusual in asymptomatic children and adolescents. This always raises the concern that they may be about to develop DM1 or already have DM2. Thus, a thorough clinical evaluation looking for insulin resistance (Table 1) and a number of studies should be carried out, including, but not restricted to, DM1-associated antibodies and C-peptide level measurement. However, a considerable proportion of these patients with persistent mild fasting hyperglycemia will have a heterozygous mutation in the glucokinase (*GCK*) gene (formerly known as MODY2)¹¹⁰. Although no large-scale population studies to assess the prevalence of *GCK* mutations have been performed, approximately 2% of pregnant women are diagnosed as having gestational

DM, and of these approximately 2-5% have a *GCK* mutation¹¹¹, which would suggest a population prevalence of 0.04-0.10%. This is the most frequent subtype of monogenic DM found in pediatric diabetes clinics.

The phenotype associated with glucokinase mutations is remarkably similar for all mutations: non-progressive, mild hyperglycemia is present from birth, but patients are asymptomatic and most remain undiagnosed until blood glucose is measured later in life⁸⁴. In addition, the following features suggest a diagnosis of a *GCK* mutation:

1. Hemoglobin A_{1c} is typically just below or just above the upper limit of the normal range.
2. If an OGTT is performed, the increment in plasma glucose levels (2-h glucose – fasting glucose) is usually small (typically <3.0 mmol/l or <55 mg/dl). However, because of the variability of the OGTT, this should not be considered an absolute criterion.
3. Parents may have 'DM2' or may not be diabetic. Testing of apparently unaffected parents' fasting glucose is important when considering a diagnosis of a glucokinase mutation. On testing, one parent will have mildly raised fasting blood glucose as this is an autosomal dominant condition.

As previously stated, fasting hyperglycemia does not deteriorate significantly, and this disorder is rarely associated with either microvascular or macrovascular complications¹¹². Thus, patients do not generally need any treatment. Pregnancy is the one exception in which hypoglycemic medication might be appropriate, but insulin is required only in cases in which there is excess fetal growth. The fetus has 50% chance of inheriting the *GCK* mutation from its mother, and the presence of the *GCK* mutation in the fetus influences its sensing of maternal glycemia. If the fetus does not inherit the *GCK* mutation it will respond to maternal hyperglycemia by excess insulin production and, therefore, excess growth; however, if the fetus does inherit the *GCK* mutation it will produce normal amounts of insulin and grow normally¹¹³. If increased fetal growth is detected it will be hard to lower the mother's glucose level (which is regulated at a raised level); thus, greater than replacement

doses of insulin will be required¹¹⁴. Early delivery is often the most helpful intervention.

Of note, the inheritance of a *GCK* mutation does not protect against the concurrent development of DM2 later in life, which occurs at a similar prevalence in those with *GCK* mutations as in the general population³⁰.

DIABETES ASSOCIATED WITH EXTRAPANCREATIC CONDITIONS

When DM in a child is associated with another multi-system disease, the possibility of a monogenic syndrome that explains all features should be considered. The most common genetic syndromes that include DM are listed below.

Syndromes affecting insulin production

1. Renal cysts and diabetes syndrome (formerly MODY5)

HNF-1 β is a transcription factor that is expressed during early embryonic development in the kidney, pancreas, liver and genital tract. Heterozygous mutations in *HNF1B* are less frequent than *HNF1A* or *HNF4A* mutations in patients with DM, but they should be considered when patients present with developmental renal disease, even in the absence of DM¹¹⁵.

The renal involvement is characterized mainly by renal cysts though a number of other presentations are possible (renal dysplasia, renal-tract malformations and/or familial hypoplastic glomerulocystic kidney disease)¹¹⁶. Genital-tract malformations, hyperuricemia and gout can also occur, as well as abnormal liver function tests^{117,118}. Half of all *HNF1B* mutation carriers have early-onset DM that presents in a similar fashion to *HNF1A* DM, but *HNF1B* mutation carriers are more insulin resistant¹¹⁹. However, *HNF1B* mutations have been described in a few patients with PNDM and TNDM^{120,121}. Evidence supports the hypothesis that the ultimate mechanism for DM in these patients may be due to pancreatic hypoplasia, as reported recently in another case¹²². The coexisting pancreatic atrophy and associated insulin resistance means that the DM of *HNF1B* mutation carriers is

not sensitive to sulfonylurea medication, and early insulin therapy is required³⁰.

There is wide variation in phenotypes even within a single pedigree, such that different combinations and severities of organ involvement are manifest among affected individuals who have identical mutations^{115,117,118,120}. Importantly, a family history of renal disease or DM is not essential to prompt a screen for this disorder, as spontaneous mutations and deletions of this gene are common (one-third to two-thirds of cases)^{115,123}.

2. Mitochondrial diabetes (maternally inherited diabetes and deafness [MIDD])

Maternally inherited DM associated with young-onset, bilateral sensorineural deafness should prompt genetic testing for the most common mitochondrial point mutation (m.3243A>G)¹²⁴.

DM in MIDD usually presents insidiously resembling DM2, but approximately 20% of patients have an acute presentation that resembles that of DM1, with ketoacidosis occurring in 8%¹²⁵. It usually presents during the third decade of life and thereafter, although it may do so earlier in patients with a high degree of heteroplasmy, and some cases in adolescents have been reported¹²⁶.

Besides DM, the same mutation can result in a number of clinical manifestations involving the most metabolically active organs. MELAS (myopathy, encephalopathy, lactic acidosis and stroke-like syndrome) is at the most severe end of the spectrum¹²⁷.

The majority of patients with MIDD are initially treated with dietary modification or oral hypoglycaemic agents, but insulin is usually required by 2 years after diagnosis. Metformin should probably be avoided because of the theoretical risk of exacerbating lactic acidosis, as metformin is known to interfere with mitochondrial function (although no cases have been reported to date)^{125,126}.

The penetrance of DM in offspring with the m.3243A>G mutation is age dependent, but is estimated to be more than 85% by the age of 70 years¹²⁵. Affected fathers should be reassured that they will not transmit the disorder to their children. An affected mother transmits the m.3243A>G mutation to all her children, even though some children may remain clinically unaffected³⁰.

In addition to the m.3243A>G mutation, early-onset DM, even during infancy, has also been described in more severe mitochondrial diseases, such as Kearns-Sayre syndrome and Pearson syndrome, but these are extremely rare^{128,129}.

3. Wolcott-Rallison syndrome

Biallelic mutations in *EIF2AK3* cause this rare autosomal recessive syndrome, which is characterized by early-onset DM, spondyloepiphyseal dysplasia, hepatic and renal failure, and developmental delay^{130,131}.

The *EIF2AK3* (eukaryotic translation initiation factor alpha 2-kinase 3) gene encodes the protein PERK (pancreatic endoplasmic reticulum kinase) that regulates the cellular response to endoplasmic reticulum (ER) stress¹³². The latter occurs when there is an imbalance between protein synthesis and protein processing, so that misfolded proteins accumulate in the ER. Pancreatic development is normal in the absence of functional protein, but misfolded proteins accumulate within the ER after birth and finally induce β -cell apoptosis. DM usually manifests during infancy, but may do so in the first 3 years of life.

4. Fanconi-Bickel syndrome

Mutations in the *SLC2A2* gene, which encodes the glucose transporter of the plasma membrane of β -cells (GLUT2), are responsible for a rare autosomal recessive syndrome characterized by abnormal metabolism of glucose and galactose, accumulation of glycogen in the liver and kidneys, and renal proximal tubular dysfunction¹³³. Usually patients have fasting hypoglycemia and postprandial hyperglycemia, but a number of cases with neonatal DM have been described^{134,135}.

5. Roger's syndrome

Thiamine-responsive megaloblastic anemia (TRMA) is an autosomal recessive disorder characterized by DM, megaloblastic anemia, and sensorineural deafness. Some patients also have congenital heart disease, optic atrophy, retinal degeneration and stroke. This disease is due to the lack of a widely-expressed cell membrane thiamine transporter

known as THTR1 and encoded by the *SLC19A2* gene¹³⁶. DM results as a consequence of diminished insulin secretion that initially, like most of the associated clinical features, responds to the administration of thiamine supplements. However, the majority of patients need insulin after puberty¹³⁷. Although the disease usually presents in toddlers and preschoolers, some cases have been reported from 3 months of age¹³⁸.

6. *Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness [DIDMOAD]).*

The association of DM with progressive optic atrophy below 16 years of age is diagnostic of this autosomal recessive syndrome¹³⁹. DM is insulin deficient and presents at a mean age of 6 years. Over time, other features develop, such as sensorineural deafness, diabetes insipidus, urinary tract dilatations, and neurological deficits. The order of appearance of the different features may vary, even within families. Patients with Wolfram syndrome die at a median age of 30 years.

The disease is produced by biallelic mutations in the gene for Wolfram syndrome (*WFS1*; 4p16.2) in at least 90% of patients¹⁴⁰. Recently, a second locus has been described (*WFS2*; 4q22-24), in association with additional symptoms such as bleeding diathesis and defective platelet aggregation, and peptic ulcer disease¹⁴¹.

Syndromes with increased insulin resistance

Monogenic DM associated with extreme insulin resistance is less frequently diagnosed than that linked with β -cell dysfunction. However, this lower prevalence might be explained in part by underdiagnosis, as the molecular background has not been fully identified and diagnostic criteria for such syndromes remain ambiguous.

1. *Insulin receptor gene mutations*

Biallelic mutations in both alleles of the insulin receptor gene (*INSR*) give rise to various very rare syndromes characterized by severe insulin resistance and greatly increased insulin and C-peptide levels, with a strong genotype-phenotype correlation existing among patients^{142,143}.

- Premature stop mutations or mutations in the extracellular domain of the receptor produce the most severe form, referred to as *Donohue syndrome* or *leprechaunism*. It is characterized by intrauterine growth retardation, disturbed glucose metabolism, and dysmorphic features (low-set ears, thick lips, flat nose root, thick skin, lack of subcutaneous fat, hypertrichosis and macrogenitalism). Most patients die during infancy.
- Less severe mutations within the intracellular domain or insulin-binding domain of the receptor lead to *Rabson-Mendenhall syndrome*. Affected patients present with dysplastic teeth and gums, thickened nails and hirsutism. Recently, association with medullary sponge kidney has been described. Most patients die before adolescence.

In both cases, patients initially have fasting hypoglycemia and postprandial hyperglycemia, but eventually develop persistent hyperglycemia and ketoacidosis.

- Type A insulin resistance syndrome affects mostly non-obese female adolescents with severe insulin resistance, acanthosis nigricans and hyperandrogenism (ranging from mild virilization to frank hirsutism). Glucose metabolism disturbances and DM usually appear later on.

Treatment of severe insulin resistance is mostly ineffective. Metabolic control remains poor and long-term complications are frequent. Approaches used include the use of insulin sensitizers, i.e. metformin and/or glitazones, but their impact is limited when the insulin resistance is very severe. Insulin is the mainstay of treatment, but extraordinarily high doses are needed, and 500 U insulin and insulin pumps are usually required. As an alternative therapeutic method, recombinant human insulin-like growth factor-I (rhIGF-I) has been reported to be successful in the treatment of Donohue syndrome and type A insulin resistance¹⁴⁴. This treatment is effective in lowering both fasting and postprandial plasma glucose concentrations, and in some cases, improvement of acanthosis nigricans was also observed; however, the long-term effect is still unsatisfactory¹⁴⁵.

2. Lipodystrophies

The main feature of lipodystrophies is a selective loss of adipose tissue. This results in a deficiency of circulating adipokines which in turn leads to significant insulin resistance¹⁴⁶.

- *Congenital generalized lipodystrophy (Berardinelli-Seip syndrome)* is a recessive disorder characterized by almost complete absence of subcutaneous and visceral fat with severe hyperinsulinemia that progresses to DM in early adolescence. In addition, patients may show acanthosis nigricans, extreme hypertriglyceridemia, fatty liver, virilization and cardiomyopathy. Mutations in two genes (*AGPAT2*¹⁴⁷ and *BSCL*¹⁴⁸) account for approximately 80% of cases¹⁴⁹. Extremely high doses of insulin are needed for metabolic control. In contrast, the response of DM to recombinant leptin can be dramatic but it is only available on a research basis¹⁵⁰.
- Patients with familial partial lipodystrophy show loss of subcutaneous fat from the extremities, lower trunk and gluteal region. They exhibit a severe insulin resistance phenotype with hyperinsulinemia, hypertriglyceridemia and decreased HDL-cholesterol. DM usually appears in late adolescence or adulthood. Heterozygous mutations in three different genes (*LMNA*, *PPARG* and *AKT2*)¹⁵¹⁻¹⁵³ have been described in this autosomal dominant condition, but additional loci are likely as many affected individuals do not have mutations in any of these genes. Insulin treatment together with metformin is still not sufficient in most cases. Due to their PPAR γ agonist effect, thiazolidinediones may be of benefit¹⁵⁴.

3. Alström syndrome

Alström syndrome is an autosomal-recessively inherited disorder that shares symptoms with Bardet-Biedl syndrome (see below), including retinitis pigmentosa, deafness, obesity, and DM. It can be distinguished from the latter syndrome by the lack of polydactyly and hypogonadism and by the absence of mental impairment¹⁵⁵. The syndrome is caused by mutations within the *ALMS1* gene of unknown function¹⁵⁶. Patients with

Alström syndrome show many features of the metabolic syndrome including hyperlipidemia, hyperuricemia, insulin resistance, hypertension, and DM. Furthermore, acanthosis nigricans, chronic active hepatitis (possibly based on non-alcoholic steatohepatitis) and dilated cardiomyopathy have been observed.

4. Bardet-Biedl syndrome

The (in most cases) autosomal-recessively inherited disorder Bardet-Biedl syndrome is characterized by mental retardation, pigmentary retinopathy, polydactyly, obesity, DM, renal dysplasia, hepatic fibrosis, and hypogonadism¹⁵⁷. Obesity is found in almost every patient, while DM affects less than 50%. 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 DM 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 at least 12 different genetic loci, referred to as BBS1 to BBS12¹⁵⁸. Heterozygous carriers possibly exhibit an increased risk for obesity, hypertension, DM, and renal disease.

CONCLUSIONS

The vast majority of children presenting with DM have DM1, and some overweight children from an ethnic minority are likely to have DM2. In contrast, monogenic DM can be identified in only 1-2% of patients. While DM1 and DM2 have no single diagnostic test, more than 80% of cases of monogenic DM can be diagnosed through genetic study.

Molecular testing is expensive, but it can have a large impact on the prognosis and treatment of both patients and their relatives. As resources are always limited, it is important to carefully select candidates through the study of available clinical data and the implementation of certain additional tests¹⁵⁹.

A complete medical history and a thorough physical examination can provide important diag-

nostic clues to a monogenic diabetes syndrome. Family history of DM is important, particularly if it is dominantly inherited or if there is a clear maternal history of DM and deafness or epilepsy (mitochondrial diabetes). Either consanguinity or a history of previous infant deaths or miscarriages point to an autosomal recessive syndrome. Additional clinical findings supporting a monogenic disease include a history of sensorineural hearing loss, visual defects or developmental delay. A history of rapid infancy-onset weight gain, removal of accessory digits, or cardiomyopathy suggests an obesity syndrome.

Useful laboratory tests in every diabetic child include autoantibodies against β -cell antigens, and fasting insulin and C-peptide to identify hyperinsulinemia. In selected patients liver and renal function tests, an audiogram, visual evoked responses, a brain MRI scan, an echocardiogram or a skeletal survey might help.

Fortunately, genetic testing for most of the conditions described above is now available with a useful resource on the International Society for Paediatric and Adolescent Diabetes (ISPAD) website (<http://www.ispad.org/>). There are already thousands of people whose fate has been improved as a result of genetic testing.

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TABLE 1Risk factors for type 2 diabetes mellitus (DM2) in children and adolescents²⁸

| |
|---|
| <p>Overweight, defined as either:</p> <ul style="list-style-type: none"> • BMI >85th percentile for age and sex • Weight for height >85th percentile • Weight >120% if ideal (50th percentile) for height |
| <p>A family history of DM2 in first- or second-degree relatives</p> |
| <p>An at-risk ethnic group:</p> <ul style="list-style-type: none"> • Native Americans • African-Americans • Hispanic-Americans • Asians • South Pacific Islanders |
| <p>Signs of insulin resistance or conditions associated with insulin resistance:</p> <ul style="list-style-type: none"> • Acanthosis nigricans • Hypertension • Dyslipidemia • Polycystic ovarian syndrome |

TABLE 2

Clinical characteristics of type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (DM2) and monogenic diabetes in children and adolescents⁵

| | DM1 | DM2 | Monogenic |
|--|---------------------------------|---|---|
| Genetics | Polygenic | Polygenic | Monogenic |
| Age | Throughout childhood | Usually pubertal (or later) | Often postpubertal except MODY2 and monogenic diabetes of infancy |
| Onset | Most often acute, rapid | Variable; from slow, mild (often insidious) to severe | Variable |
| Associations: | | | |
| Autoimmunity | Yes | No | No |
| Ketosis | Common | Rare | Rare in MODY, not uncommon in neonatal diabetes |
| Obesity | Same risk as general population | Yes | Same risk as general population |
| Acanthosis nigricans | No | Yes | No |
| Frequency (% of all DM in young people) | Usually >95% | Most countries: <5-10% (60-80% in Japan) | 1-3% |
| Diabetic parent | 2-4% | 80% | 90% |

TABLE 3

Clinical characteristics of probands with transient neonatal diabetes (TNDM) grouped by genetic etiology

| Characteristic | 6q24 | ABCC8 | KCNJ11 | p value |
|--|------------------------|------------------------|------------------------|----------------|
| Proportion of TNDM cases (%) | 71% | 13% | 12% | <0.05 |
| Sex (% male) | 53 | 54 | 58 | NS |
| Gestational age (weeks) | 40 (36-42) | 39 (30-41) | 38 (30-40) | NS |
| Birth weight (g) | 1,950 (1,600-2,670) | 2,575 (1,360-3,400) | 2,570 (1,535-3,570) | <0.05 |
| Age at diagnosis (weeks) | 0 (0-4) | 4 (0-9) | 5 (0-16) | <0.05 |
| Age at remission (weeks) | 13 (5-60) | 22 (7-52) | 45 (2-208) | <0.05 |
| Age when entering study (years) | 12 (1-36) | 5 (0.84-16) | 7.5 (0.84-17) | – |
| Diabetes relapse (%) | 30 | 0 | 33 | – |
| Age at relapse (years) | 16 (4-25) | – | 4.7 (3-15) | – |

Adapted from ³³.

TABLE 4Comparison of the clinical characteristics of *INS*, *KCNJ11* and *ABCC8* mutation carriers

| Characteristic | <i>KCNJ11</i> | <i>ABCC8</i> | <i>INS</i> | p value |
|-------------------------------------|------------------------|------------------------|------------------------|----------------|
| Proportion of PNDM cases (%) | 31 | 10 | 12 | <0.05 |
| Sex (% male) | 53 | 42 | 50 | NS |
| Gestational age (weeks) | 40 (33-42) | 40 (26-40) | 40 (35-42) | NS |
| Birth weight (g) | 2,660 (1,850-3,600) | 2,700 (1,510-4,200) | 2,700 (1,700-3,900) | NS |
| Age at diagnosis (weeks) | 8 (0-33) | 8 (0-40) | 11 (0-1,144) | <0.05 |

Adapted from ⁴⁵.

PNDM = permanent neonatal diabetes.

TABLE 5
Causes of neonatal diabetes mellitus

| Gene | Locus | Inheritance | Associated clinical features |
|--|---------------|--------------------------|---|
| Disturbed pancreatic development: | | | |
| <i>ZAC</i> | 6q24 | Variable (imprinting) | TNDM ± macroglossia |
| <i>IPF1</i> | 13q12.1 | AR | Pancreatic agenesis |
| <i>PTF1A</i> | 10p12.3 | AR | Pancreatic agenesis and cerebellar hypoplasia |
| <i>HNF1B</i> | 17cen-q21.3 | AD | Pancreatic hypoplasia and renal cysts |
| <i>GLIS3</i> | 9p24.3-p23 | AR | Congenital hypothyroidism, liver fibrosis and polycystic kidneys |
| Reduced β-cell function: | | | |
| <i>KCNJ11</i> | 11p15.1 | AD | TNDM/PNDM ± DEND |
| <i>ABCC8</i> | 11p15.1 | AD, AR | TNDM/PNDM ± DEND |
| <i>GCK</i> | 7p15-p13 | AR | Isolated PNDM |
| <i>SLC2A2</i> (GLUT2) | 3q26.1-q26.3 | AR | Fanconi-Bickel syndrome (hypergalactosemia and hepatic failure) |
| <i>SLC19A2</i> | 1q23.3 | AR | Roger's or TRMA syndrome (thiamine responsive megaloblastic anemia, sensorineural deafness) |
| Increased β-cell destruction: | | | |
| <i>INS</i> | 11p15.1 | AD | Isolated PNDM |
| <i>EIF2AK3</i> (PERK) | 2p12 | AR | Wollcott-Rallison syndrome (spondyloepiphyseal dysplasia, recurrent hepatitis, renal failure, mental retardation) |
| <i>FOXP3</i> | Xp11.23-p13.3 | X-linked | IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, elevated IgE) |

AR = autosomal recessive; AD = autosomal dominant; TNDM = transient neonatal diabetes mellitus; PNDM = permanent neonatal diabetes mellitus; DEND = syndrome of developmental delay, epilepsy and neonatal diabetes.