Published in final edited form as:

Curr Diab Rep. 2011 December ; 11(6): 519–532. doi:10.1007/s11892-011-0234-7.

Neonatal Diabetes: An Expanding List of Genes Allows for Improved Diagnosis and Treatment

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Abstract

There has been major progress in recent years uncovering the genetic causes of diabetes presenting in the first year of life. Twenty genes have been identified to date. The most common causes accounting for the majority of cases are mutations in the genes encoding the two subunits of the ATP-sensitive potassium channel (K_{ATP}), *KCNJ11* and *ABCC8*, and the insulin gene (*INS*), as well as abnormalities in chromosome 6q24. Patients with activating mutations in *KCNJ11* and *ABCC8* can be treated with oral sulfonylureas in lieu of insulin injections. This compelling example of personalized genetic medicine leading to improved glucose regulation and quality of life may—with continued research—be repeated for other forms of neonatal diabetes in the future.

Keywords

Neonatal diabetes; Monogenic diabetes; NDM; PNDM; TNDM; MODY; *KCNJ11*; *ABCC8*; K_{ATP} ; *INS*; 6q24; *EIF2AK3*; *GCK*; *PDX1*; *FOXP3*; *IPEX*; *PTF1A*; *RFX6*; *NEUROG3*; *NEUROD1*; *WFS1*; *DIDMOAD*; *SLC19A2*; *TRMA*; *SLC2A2*; *GLIS3*; *HNF1B*; *IER3IP1*

Introduction

Diabetes mellitus is an etiologically heterogeneous disorder. The most common forms, type 1 and type 2 diabetes, are multifactorial with variation in a number of genes (polygenic) together with nongenetic factors leading to disease. However, 1% to 2% of all cases result from mutations in a single gene (monogenic) that are sufficient to cause diabetes. In particular, diabetes occurring under 6 months of age—usually termed *neonatal diabetes*—appears to be predominantly monogenic and the fraction of cases without a known cause is diminishing rapidly as new genes are discovered (Table 1). Because many of these monogenic causes have also been found to cause diabetes after 6 months of age, we prefer the term *congenital diabetes*, which emphasizes the genetic nature of this group of disorders rather than the age of onset; however, for consistency with existing literature, we continue the use of the term neonatal diabetes.

The neonatal diabetes phenotype encapsulates numerous subtypes, wherein most etiologies involve a severe disruption in β -cell function. Neonatal diabetes can be permanent and require lifelong treatment, or may be transient, in which case the diabetes may spontaneously remit (or be so mild as not to require treatment), but will often relapse,

usually during adolescence. Although the majority of cases of neonatal diabetes involve isolated diabetes, many of the known monogenic causes are characterized by a variety of syndromic features. Increased attention to the primarily genetic nature of early-onset diabetes has resulted in an expanding list of causal genes, as well as an expansion of phenotypic characteristics in syndromic forms. This list includes some genes that more often cause diabetes that is diagnosed beyond the neonatal period, thus supporting the consideration of all monogenic diabetes gene causes in the differential diagnosis of early-onset diabetes, guided when possible by other clinical features (Table 2).

We briefly review here the known genetic causes of diabetes occurring in the first year of life. In addition, we focus on recent reports to highlight newer aspects of the most common forms of neonatal diabetes caused by mutations in *KCNJ11*, *INS*, and *ABCC8*, as well as some general considerations in the diagnosis, treatment, and prognosis of these disorders.

***KCNJ11/ABCC8*: Neonatal Diabetes due to Activating Mutations of the K_{ATP} Channel**

Nearly half of all cases of permanent neonatal diabetes are due to activating mutations in *KCNJ11* or *ABCC8*; their diabetes can be remarkably well controlled by oral sulfonylurea tablets instead of injected insulin [1, 2]. These discoveries have led to a renewed interest in neonatal diabetes, not only in the scientific community, but also among individual clinicians, families, and even the general public, who have been struck by the compelling stories told about lives changed by a remarkable simplification of treatment that no longer requires multiple daily insulin injections. Although this realization of the promise of personalized medicine may not affect a large number of patients, it has had a large impact on the relatively small number of patients concerned. In most such cases, transition from insulin to sulfonylurea therapy is best done during an inpatient admission using published guidelines [2], with advice sought from recognized centers with extensive experience. Although the resulting treatment is clearly easier and the level of diabetes control better, many questions still remain to be clarified:

1. How sustainable will treatment with oral sulfonylureas be, and will age, obesity, or other factors eventually require supplemental insulin or other medications? In this regard, a single case has been fortuitously treated for over 50 years [1]. Furthermore, our cases [3] and those reported by others [4] all continue to do well and give reason for optimism, but only time and careful tracking of long-term outcome will tell.
2. How often will patients have hypoglycemia, and what happens to their blood sugar levels during illness, procedures, or hospitalization, especially if oral medications cannot be taken? The incidence of hypoglycemia seems to be remarkably low despite the high levels of sulfonylureas that stimulate closure of the ATP-sensitive potassium channel (K_{ATP}) channel. Only one case has been reported to have had an episode of severe hypoglycemia, which has also been very rare among our patients [5]. Glucose levels must be monitored carefully in these patients during illness or when not eating, because blood glucose levels will be difficult to predict. Anecdotally, subjects within our Registry have variably reported mild hypoglycemia or hyperglycemia during illness, although none has reported requiring supplemental insulin (Greeley et al., Unpublished data).
3. To what extent will neurodevelopmental effects be improved or even prevented by sulfonylurea treatment? In this regard a notable study recently confirmed that mice with brain expression of a mutant form of the protein encoded by *KCNJ11* (Kir6.2) have a neurologic pheno-type reminiscent of patients with the same mutation

(V59M) [6•]. These results support anecdotal evidence that pharmacologic blockade may improve neurodevelopmental outcomes but will likely depend on passage of the drug across the blood-brain barrier. Our experience has been in line with that of others, suggesting a modest improvement in neurologic sequelae after treatment with sulfonylureas; however, long-term studies using standardized measures are needed to substantiate the presumed benefit, especially in those starting treatment at very early ages. Such potential benefit should be considered in individuals who continue to require insulin despite sulfonylurea treatment.

Such questions and many others are being addressed through efforts such as our Neonatal Diabetes Registry (<http://NeonatalDiabetes.org>) to track long-term outcomes in as many patients as possible [7]. Over 70 subjects from North America are now included within the Registry who have mutations in *KCNJ11* or *ABCC8*, and more are added each month. Rare cases (usually older patients) who have not had complete success with sulfonylureas have shown benefit from other oral agents, such as dipeptidyl peptidase 4 inhibitors [3]; nevertheless, in the absence of a randomized controlled trial it will be difficult to make firm recommendations regarding their use in the treatment of this form of diabetes. The observation that older patients may not as easily achieve insulin independence is corroborated by mouse models suggesting a loss of β -cell mass over time [8, 9]. Thus, even if the cells that remain are able to regain full function, there may not be enough β cells in some patients to achieve insulin independence. Further research is needed to establish the dependence upon age or other factors, such as the particular mutation involved, in determining the likelihood of sulfonylurea responsiveness. Fortunately, the majority of the patients with activating mutations in *KCNJ11* and *ABCC8*, regardless of age at genetic diagnosis and years of insulin therapy, can be switched to oral agents.

***INS*: Diabetes Caused by Mutations in the Insulin Gene**

Heterozygous autosomal dominantly inherited mutations in the insulin gene (*INS*) are the second most common cause of permanent neonatal diabetes (after mutations in *KCNJ11*), with diagnosis of diabetes sometimes occurring after 6 months of age [10–15]. The original suggested mechanism involving β -cell endoplasmic reticulum stress due to misfolding of the protein encoded by the mutated allele has been upheld in experiments utilizing in vitro cell expression as well as mouse models [16–21]. Further study of populations diagnosed outside the neonatal period has revealed that *INS* mutations may also be found in patients with a diagnosis of type 1B (antibody-negative) diabetes [13]. Although these studies consistently revealed that approximately 10% of patients diagnosed clinically as having type 1 diabetes are autoantibody-negative, they varied in the incidence of *INS* mutations in these patients: 2/7, 2/25, and 0/24 [22–24]. Although the overall proportion of *INS* mutations in those clinically diagnosed with type 1 diabetes was quite low (4/812 or 0.5%), they represented a significant proportion of the antibody-negative subset (7%), further justifying antibody testing as a routine part of clinical diabetes diagnosis and management. It is unclear whether *INS* mutations ever cause antibody-positive type 1 diabetes.

Similar studies have suggested that *INS* mutations may also be a rare cause of maturity-onset diabetes of the young (MODY) [13, 18, 25]. The location of mutations causing later-onset diabetes in the signal peptide of preproinsulin is distinct from the location of those causing neonatal diabetes (often of cysteine residues involved in proinsulin folding), and suggests that different pathophysiologic mechanisms may be involved; however, other mutations causing later-onset diabetes are in similar locations as those causing neonatal diabetes but may cause more mild dysfunction [26].

Recessively acting mutations that impair *INS* gene expression through various mechanisms also cause permanent or transient neonatal diabetes [27]. Finally, large deletions in *INS* were

recently described to cause neonatal diabetes characterized by complete insulin deficiency [28]. Of note, a high rate of adult-onset diabetes not associated with obesity was seen in family members carrying one copy of an *INS* deletion [28]. Another interesting observation is that children who inherit *INS* mutations from their fathers seem to have an earlier onset of diabetes than those who inherited such mutations from their mothers, which the authors suggest may arise from preferential silencing of maternally inherited mutant allele by imprinting effects at the *INS-IGF2* locus [29].

6q24: Transient Neonatal Diabetes Related to Overexpression of Imprinted Genes

Transient neonatal diabetes characterized by severe intrauterine growth restriction and diagnosis of diabetes within days of life is most often related to overexpression of associated paternally imprinted genes at chromosome 6q24 [30]. This is due to uniparental paternal disomy, a paternally inherited duplication, or a maternal methylation defect, such as from recessive mutations in *ZFP57* [31]. Regardless of mechanism, these cases exhibit diabetes that resolves spontaneously within a few months, only to return later in life (usually adolescence). The treatment of these patients has typically relied on insulin, but some suggestion of a benefit of oral sulfonylureas has been made [32].

In contrast, transient forms of neonatal diabetes may also be caused by mildly activating mutations in *ABCC8* and *KCNJ11*, but in these cases the clinical course is often less predictable and characterized by relapsing/remitting diabetes that may require treatment intermittently through childhood [33–35]. In many of these families, parents or other relatives have adult-onset diabetes associated with the same mutation but any hypothetical neonatal hyperglycemia was probably not assessed soon after birth. Furthermore, some patients within the same family have been described to have transient or permanent neonatal diabetes, suggesting the presence of other factors (genetic or environmental) that can modify the diabetes phenotype. They could also be considered a form of MODY and recent studies would support the notion of screening for *ABCC8* mutations in patients with a mild adult-onset or antibody-negative diabetes [24, 36]. As described elsewhere, very rare mutations in *HNF1B* or recessive mutations in the promoter/enhancer region of *INS* may also cause a phenotype that could be described as transient neonatal diabetes. However, 6q24-related diabetes seems to be most consistently characterized by a long remission phase, whereas other genetic causes seem to involve inconsistent episodes during which treatment may not be required.

Recessive and/or Syndromic Causes of Congenital Diabetes

***RFX6*: Syndrome of Diabetes, Intestinal Atresia, Gall Bladder Hypoplasia, and Diarrhea**

Rare patients have been described with a syndrome characterized by diabetes within the first few days of life: pancreatic hypoplasia, intestinal atresia, gall bladder agenesis/hypoplasia, and congenital diarrhea [37–39]. Five out of six such cases were subsequently reported to carry homozygous mutations in *RFX6*, highlighting the role of this transcription factor as a key regulator of β -cell differentiation [40•]. Human cases for which pathology specimens were available were strikingly similar to knockout mice in having chromogranin A-positive islet cells, but negative staining for insulin, glucagon, and somatostatin. Despite relative hypoplasia of the small-appearing pancreata, pancreatic exocrine function appeared to be intact in these patients, and their intractable diarrhea was unresponsive to pancreatic enzyme replacement.

***IER3IP1*: Syndrome of Neonatal Diabetes with Microcephaly and Infantile Seizures**

Infants in two unrelated consanguineous families exhibited a similar phenotype of neonatal diabetes with simplified gyral pattern microcephaly and severe infantile-onset epileptic encephalopathy. Linkage analysis led to sequencing of *IER3IP1*, revealing two different missense mutations at conserved positions predicted to be damaging [41•]. Pathology specimens of one case revealed widespread apoptotic neurons within a very small brain and greatly reduced numbers of insulin-positive pancreatic islet cells. In vitro studies suggested a role for *IER3IP1* in protecting cells from stress-induced apoptosis.

***NEUROG3*: Syndrome of Intractable Diarrhea from Birth with Early-Onset Diabetes**

A total of five cases with diabetes and chronic intractable malabsorptive diarrhea that started soon after birth have now been reported to have recessive mutations in *NEUROG3* [42•, 43•]. Two recently reported cases had moderate hyperglycemia starting soon after birth that was treated with insulin at 20 days and 5 months of age. These two carried nonsense mutations whereas three cases originally reported with isolated diarrhea due to missense mutations later also developed insulin-requiring diabetes by 9 years of age [44]. These cases confirm a key role for *NEUROG3* not only in β cells, but also in the development and function of enteroendocrine cells, which appeared completely absent in biopsy specimens from these patients, similar to *NEUROG3* $-/-$ mice. Importantly, the pancreas in all human cases appeared normal by imaging and only one case exhibited any evidence of exocrine pancreatic dysfunction, with the severe diarrhea exhibiting only limited improvement with pancreatic enzyme replacement.

***NEUROD1*: Syndrome of Diabetes with Cerebellar Hypoplasia without Pancreatic Exocrine Dysfunction**

NEUROD1 is a basic helix-loop-helix (bHLH) transcription factor that is highly expressed in both developing and mature β cells; very rare cases of MODY have been attributed to heterozygous mutations in this gene [45]. More recently, two small for gestational age cases with neonatal diabetes by 2 months of age were described to exhibit cerebellar hypoplasia, developmental delay, sensorineural deafness, and visual impairment. They were found to carry two different homozygous frameshift mutations resulting in a truncated NeuroD1 protein lacking the activation domain [46•]. These patients were reported to have a normally sized pancreas with no evidence for pancreatic exocrine dysfunction and were not described to have gastrointestinal problems.

***PTF1A*: Syndrome of Diabetes with Cerebellar and Pancreatic Hypoplasia with Exocrine Dysfunction**

PTF1A encodes a bHLH transcription factor that is essential for specification of pancreatic endocrine, exocrine, and ductal cells. Five cases in two families were found to carry two different homozygous truncating mutations in *PTF1A* causing a syndrome of congenital diabetes involving flexion contractures of arms and legs, paucity of subcutaneous fat and optic nerve hypoplasia, in addition to complete agenesis of the cerebellum and complete absence of the pancreas, a finding which was confirmed by extensive postmortem macro- and microscopic examination [47, 48]. Despite this, circulating C-peptide and insulin levels were low but detectable; however, the location of the insulin-producing cells was not determined. Those with *NEUROD1* mutations also have cerebellar agenesis but have not been reported to have pancreatic agenesis as in those with *PTF1A* mutations, who also exhibit clinically apparent pancreatic exocrine dysfunction. Another case from Turkey was recently reported with this very rare recessive syndrome due to *PTF1A* mutations and also had detectable C-peptide and insulin levels during severe hyperglycemia [49].

***GLIS3*: Syndrome of Diabetes and Congenital Hypothyroidism**

Six individuals in three families with a syndrome of neonatal diabetes within the first few days of life, low birth weight, mild facial dysmorphism, and congenital primary hypothyroidism were found to have homozygous abnormalities of *GLIS3*, encoding a Krüppel-like zinc finger protein [50]. Of note, the one family with a frameshift insertion mutation also exhibited liver fibrosis and polycystic kidneys, the latter of which is also seen in mouse models [51, 52]. The two other families carried large homozygous deletions upstream of *GLIS3* that abrogated pancreatic but not kidney expression, and these patients did not have renal cysts. Recently, a second report described an additional two cases within two families carrying two different large homozygous deletions that included the first few exons of *GLIS3*, although the parents in one family were not known to be related [53]. Interestingly, both of these cases displayed a severe phenotype similar to those with missense mutations in the original report, including liver fibrosis and renal cysts. In addition, one of these cases exhibited osteopenia and deafness, and both were found to have pancreatic exocrine insufficiency that responded to enzyme replacement therapy.

***PDX1*: Syndrome of Congenital Diabetes with Pancreatic Hypoplasia and Exocrine Dysfunction**

Homozygous mutations in *PDX1* leading to pancreatic agenesis was the first discovered genetic cause of permanent neonatal diabetes, found through investigation of a proband whose parents were consanguineous and part of a very large pedigree exhibiting a high frequency of adult-onset diabetes/MODY [54–56]. Another proband carrying the same homozygous Pro63fsX60 mutation was recently described and may be related to the original family [57, 58]. The recent case underwent CT and multiple ultrasound examinations that were interpreted by the authors as consistent with the presence of only an underdeveloped head of the pancreas. In light of these findings, the ultrasound of the original case was also reinterpreted to have some pancreatic head tissue present as well. A separate case with a similar phenotype was found to have compound heterozygous missense mutations in *PDX1* but the pancreas was described as absent [59]. All three of these cases had clinically apparent pancreatic exocrine insufficiency that responded well to enzyme replacement therapy. In contrast, two additional cases who were related to each other (first cousins) exhibited isolated neonatal diabetes without clinical evidence of exocrine dysfunction and were found to carry a novel homozygous hypomorphic mutation in *PDX1* [60]. Biochemical testing revealed evidence for mild subclinical pancreatic exocrine dysfunction that did not require enzyme replacement. Ultrasound examinations revealed normal pancreatic tissue in one case and only the pancreatic head in the other case. It is worth mentioning that although *PDX1* mutations are described as a cause of MODY4, sequencing of 910 subjects with type 2 diabetes and 878 controls revealed that 5% of both populations carried low-frequency *PDX1* variants that were not associated with the diabetes phenotype, suggesting that mutations in *PDX1* are a rare cause of diabetes [61•].

***HNF1B*: Neonatal Diabetes with Renal Anomalies**

Only two cases of neonatal diabetes have been reported to be caused by heterozygous mutations in *HNF1B*, although such mutations, or large deletions, have long been described as a cause of later-onset diabetes with renal and/or genitourinary abnormalities (renal cysts and diabetes syndrome, RCAD, or MODY5). In the first report, a child who was very small for gestational age presented with severe diabetic ketoacidosis at 15 days of life but subsequently required insulin only intermittently until 6 years of age, after which she was insulin dependent [62]. Her younger brother had a normal birth weight but malformed kidneys necessitating transplant at 3 years of age, with only one transient episode of hyperglycemia during illness that resolved without treatment. Their clinically unaffected mother was found to carry the same *HNF1B* mutation (S148W) as her children at a low

level, suggesting genetic mosaicism. The second report found mutation S148L in a case with very low birth weight requiring hospital admission with monitoring of blood glucose that became elevated only at 17 days of life and required insulin treatment for only 6 days [63]. Diabetes recurred at 8 years of age and was initially treated with tolbutamide but thereafter required insulin. He was also noted to have small dysplastic kidneys (without cysts or evidence of renal failure), pancreatic hypoplasia, and biochemical evidence of reduced pancreatic exocrine dysfunction. Interestingly, a cohort of five patients from two families with *HNF1B* mutations were all found to have mild pancreatic exocrine insufficiency and hypoplastic pancreata characterized by presence of only the head, with absence of any detectable body or tail [64]. In relation to these neonatal cases with a form of relapsing/remitting diabetes, it is interesting to note the incomplete penetrance of diabetes in family members known to carry an *HNF1B* deletion or mutation, in whom the most consistent feature is a renal anomaly, especially cysts.

PAX6: Syndrome of Neonatal Diabetes with Brain Malformations, Microcephaly, and Microphthalmia

Heterozygous mutations in *PAX6*, a paired domain-containing transcription factor involved in islet cell differentiation and function, have been described as a cause of ocular anomalies such as aniridia, and members of families carrying *PAX6* mutations also exhibit impaired glucose tolerance and diabetes later in life [65]. In one study, mutation carriers in one large family were found to have high proinsulin/total insulin levels in response to glucose challenge even before the onset of diabetes, suggesting a mechanism corroborated in a similar mouse model related to the effect of *PAX6* on proinsulin processing through regulation of PC1/3 expression [66]. Only two cases carrying biallelic mutations in *PAX6* have been reported: the first case died at 1 week of life and exhibited severe brain malformations, microcephaly, and anophthalmia, without mention of hyperglycemia. Another surviving case had brain malformations, microcephaly, microphthalmia, and panhypopituitarism, along with neonatal-onset diabetes treated with insulin, despite normal appearing pancreas on MRI [67]. A brother of this case who died in infancy also had anophthalmia and neonatal diabetes.

WFS1: Syndrome of Diabetes with Optic Atrophy, Diabetes Insipidus, and/or Deafness

Several large case series have reported onset of diabetes as the earliest and most consistent feature of Wolfram syndrome, with subsequent development of optic atrophy, then later onset of diabetes insipidus and/or deafness (DIDMOAD syndrome). Recessive mutations in the large *WFS1* gene were described as the cause of the neurodegenerative diabetes syndrome but such mutations are quite heterogeneous and do not clearly predict associated phenotypic features [68, 69]. In vitro studies and rodent models suggest that *WFS1* downregulates endoplasmic reticulum stress and that a reduction in its activity leads to increased apoptosis in β cells and other tissues [70, 71]. Of note, some isolated features, such as diabetes, deafness, optic atrophy, and psychiatric problems, have been reported in heterozygous carriers of sequence variants, such as within families affected by Wolfram syndrome [72, 73]. Although diabetes is most often diagnosed in early childhood (median age, 4.3–6 years in European populations), several cases have been reported with diabetes recognized in the first year of life, as early as 3 weeks of age [74, 75]. Thus, although it has not usually been described as a cause of neonatal diabetes, mutations in *WFS1* should be considered in patients with early-onset diabetes mellitus, particularly if they develop optic atrophy, diabetes insipidus, and/or deafness.

SLC19A2: Diabetes as Part of Thiamine-Responsive Megaloblastic Anemia Syndrome

The gene *SLC19A2* encodes a plasma membrane thiamine transporter, THTR1, and has been reported as the cause of thiamine-responsive megaloblastic anemia (Rogers syndrome), with

diabetes often diagnosed well after the neonatal period. Although at least 10 previously reported cases with *SLC19A2* mutations were diagnosed with early-onset diabetes between 2 and 12 months of age, it has not often been mentioned as a neonatal diabetes gene. Mutations in *SLC19A2* should be considered in any patient with megaloblastic anemia and diabetes, or especially with the complete triad including sensorineural deafness. Interestingly, in addition to the anemia, the diabetes has also been described to exhibit a variable degree of improvement in response to thiamine treatment [76–79]. Although most reports describe the deafness as being irreversible, one case treated before 2 months had apparent amelioration of deafness, further highlighting the importance of an early genetic diagnosis to guide appropriate treatment [80].

***SLC2A2/GLUT2*: A Rare Cause of Early-Onset Diabetes as Part of Fanconi-Bickel Syndrome**

Fanconi-Bickel syndrome (FBS) was originally described in 1949, and was later found to be due to homozygous or compound heterozygous mutations in the gene *SLC2A2*, encoding the facilitative glucose transporter, GLUT2 [81–83]. FBS involves hepatomegaly related to hepatic and renal glycogen accumulation; renal proximal tubular dysfunction characterized by glucosuria, as well as phosphate wasting often leading to hypophosphatemic rickets; delay of puberty and short stature; hypergalactosemia; and mild fasting hypoglycemia but postprandial hyperglycemia and diabetes or impaired glucose tolerance [84]. As such, the elevated glucose levels have in some cases been detected in patients well under 1 year of age and FBS should thus be considered in the differential diagnosis of neonatal diabetes when any characteristic features are present [85]. The characteristic galactosemia may also be detected during the neonatal period by newborn screening programs, and when other features are present, genetic testing of *SLC2A2* may lead to an early diagnosis [86, 87].

***FOXP3*: Immunodysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX) Syndrome**

Mutations in the X-linked gene *FOXP3* are a rare cause of neonatal monogenic autoimmune diabetes, along with numerous other features including enteropathy causing severe diarrhea and malnutrition, severe eczema, and autoimmune thyroid disease. Although patients with the classically described syndrome have a severe clinical course usually resulting in death within the first few years of life without stem cell transplant, other patients have a milder phenotype and a few have lived into childhood or beyond [88]. This phenotypic variability may be related to the specific mutations or other unknown factors and suggests consideration of *FOXP3* sequencing in cases that may not fit all of the features of the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome.

***EIF2AK3*: Syndrome of Diabetes with Epiphyseal Dysplasia and Episodic Liver or Renal Dysfunction**

Wolcott-Rallison syndrome (WRS) was originally described in three siblings in 1972, and later was found to be due to recessive mutations in *EIF2AK3* [89, 90]. This gene encodes a translation-regulating kinase present in many tissues that plays an important role in trafficking of proinsulin through the secretory pathway in β cells [91]. The clinical details of past cases were recently reviewed [92], in addition to a report of the largest series of 29 cases within 25 families [93]. Although most cases are homozygous, compound heterozygous cases have been described and consanguinity may not be known. Thus, because epiphyseal dysplasia (the most consistent feature of WRS) may not be apparent clinically, radiographs could be considered to help guide genetic testing in any case of neonatal diabetes without a known cause.

GCK: Isolated Congenital Diabetes due to Recessive Mutations

Recessive mutations in the gene encoding the glycolytic enzyme glucokinase (*GCK*) were the second described cause of permanent neonatal diabetes [94]. A total of 14 cases have been reported and none were noted to have any evidence for pancreatic hypoplasia or exocrine deficiency, nor any extrapancreatic features, aside from being very small for gestational age (only one case 10th percentile, all others <3rd percentile). One recently reported case was highly unusual in carrying only one heterozygous mutation, with no deletions detected, nor any mutations in other neonatal diabetes genes [95]. Despite the typical mild presentation of family members from her large pedigree, she presented with severe hyperglycemia and ketoacidosis on the 2nd day of life and has since had hemoglobin A_{1c} levels greater than 8% despite replacement doses of insulin (0.6–0.8 U/kg/day). The mechanism for the severity of phenotype in this case remains unclear but could involve mosaic inactivation of the normal allele in β cells. Of note, three of the cases have been reported to exhibit partial responsiveness to repaglinide [96] or the sulfonylurea glibenclamide (glyburide, doses 0.85–1 mg/kg/day) [97, 98], suggesting that sulfonylurea inhibition of the K_{ATP} channel may allow for insulin secretion despite the lack of glucose responsiveness related to their *GCK* deficiency. Although mutations in *GCK* are a rare cause of neonatal diabetes, it should be considered in cases with isolated diabetes, especially if consanguinity is suspected and/or family members have a *GCK-MODY* (*MODY2*) phenotype.

General Considerations regarding Diagnosis and Etiology of Neonatal Diabetes

Cost-Effectiveness of Genetic Testing in K_{ATP}-Related Neonatal Diabetes

We recently published an analysis of the cost-effectiveness of genetic testing in patients diagnosed with diabetes under 6 months of age. Given the high likelihood of *KCNJ11* or *ABCC8* mutations in this population, and the resulting improvements in diabetes control, quality of life, and lower costs of treatment, we found that there would be significant cost-savings resulting from a policy of testing compared with a policy of no genetic testing in this population of patients [99••]. This is a highly unusual situation for cost-effectiveness analyses, in that not only does this advance in medical diagnosis and treatment result in an improved outcome, but it does so at a decreased cost. Furthermore, a threshold analysis allowed us to estimate that for the testing policy to remain cost-effective for any population being tested, the prevalence of *KCNJ11* or *ABCC8* mutations would need be at least 0.3%. Since a few such cases have now been reported to have been diagnosed between 6 and 12 months of age, it is quite possible that testing this group may also be appropriate [15, 100]. Because such cases are often selected for being negative for diabetes-related autoantibodies, further research is required to more definitively determine the prevalence of mutations in later age groups, especially as a few cases have been reported to have positive antibodies [3, 101]. Inevitable decrease in the cost of genetic testing will also favor a broadening of the screening for mutations in these genes.

The Future of Genetic Testing in Neonatal Diabetes

Given the long list of genes now known to cause congenital diabetes, it has become increasingly time consuming, labor intensive, and expensive to sequence all possible genes using traditional methods. Even sequencing the three most commonly mutated genes is costly, given that *ABCC8* is very large, with 39 exons. Furthermore, the choice of genes to be tested using this approach relies on the availability of reliable and comprehensive phenotypic information, although such features may be subclinical (Tables 1 and 2). At least 60% to 75% of probands diagnosed under 6 months of age will have an identifiable genetic

cause using the standard approach, with this proportion being influenced by factors such as the frequency of consanguinity within the population being tested and whether all possible genes were considered even in the absence of clear syndromic features [3, 11, 15]. In this regard, next-generation sequencing and informatics approaches are likely to quickly become the standard for screening for sequence variants in any number of genes. We have successfully begun this approach, and others have also demonstrated that standard commercial platforms for whole-exome sequencing have sufficient coverage of the genes of interest for neonatal diabetes [102•].

In using high-throughput sequencing as a screening tool, it will be important to utilize informatics strategies that will minimize the chance that any possible causative variant could be missed. Although doing so may increase the likelihood of false-positive results, any variants found should still be confirmed by traditional methods. In addition to being a more cost-effective and efficient approach for screening of known genes, it is quite likely that new genetic causes for patients with unknown etiologies will result, particularly with the advent of affordable whole-genome sequencing. As the cost of these techniques lowers, our cost-effectiveness study would support the expansion of testing into other populations of diabetes patients who may be much less likely to have mutations that are treatable with sulfonylureas but may still benefit from uncovering a genetic diagnosis.

Conclusions

Mutations in 20 genes are now known to cause diabetes presenting in the first year of life. However, we and others have been able to find a genetic cause in only 60% to 75% of patients with permanent neonatal diabetes diagnosed under 6 months, suggesting that continuing research will identify new genes. Anyone diagnosed under 6 months of age should have comprehensive genetic testing guided by clinical features (Tables 1 and 2); however, the optimal cost-effective algorithm for consideration of testing in those diagnosed after 6 months of age remains unclear but should be considered in any case with negative antibody testing, syndromic features, or a strong family history of diabetes. Concurrent with the expansion in the number of known genes has been an extension of the known phenotypic spectrum of various syndromic etiologies as well as overlap between genes associated with neonatal diabetes and MODY. Decreasing costs of DNA sequencing will allow genetic testing to become routine in the diagnosis of neonatal diabetes. Furthermore, future advances in understanding the pathophysiology of other causes of congenital diabetes will hopefully lead to more effective cause-specific treatments.

Acknowledgments

The authors wish to thank all the wonderful patients and families participating in our Monogenic Diabetes Registry (<http://MonogenicDiabetes.org>) studies. Research at the University of Chicago Kovler Monogenic Diabetes Center is supported through funding provided by the US National Institutes of Health Clinical and Translational Science Awards UL1RR024999 and Diabetes Research and Training Center P60 DK020595 programs, as well as the American Diabetes Association (1-11-CT-41), the Lewis-Sebring Family Foundation, and the Kovler Family Foundation.

Disclosure Conflicts of interest: S.A.W. Greeley: is supported by the Lewis-Sebring Family Foundation as the Lewis-Sebring Fellow in Diabetes Genetics, as well as from the Kovler Family Foundation; R. N. Naylor: is supported by a minority fellowship award (7-10-MI-08) from the American Diabetes Association, the Lewis-Sebring Family Foundation, and the Kovler Family Foundation; L.H. Philipson: is supported by the Lewis-Sebring Family Foundation and the Kovler Family Foundation; G.I. Bell: is supported by the Lewis-Sebring Family Foundation and the Kovler Family Foundation; also, the University of Chicago receives royalties from Correlagen Diagnostics for genetic testing for mutations in the diabetes genes *GCK*, *HNF1A*, *HNF1B* and *HNF4A*, based on patents 5,541,060 and 6,187,533, resulting from prior research by Dr. Bell.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Gloyn AL, Pearson ER, Antcliff JF, 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):1838–1849. [PubMed: 15115830]
2. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*. 2006; 355(5):467–477. [PubMed: 16885550]
3. Støy J, Greeley SAW, Paz VP, et al. Diagnosis and treatment of neonatal diabetes: a United States experience. *Pediatr Diabetes*. 2008; 9(5):450–459. [PubMed: 18662362]
4. Iafusco D, Bizzarri C, Cadario F, et al. No beta cell desensitisation after a median of 68 months on glibenclamide therapy in patients with *KCNJ11*-associated permanent neonatal diabetes. *Diabetologia*. 2011 Aug 7. PMID: 21822789;
5. Rafiq M, Flanagan SE, Patch A-M, et al. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. *Diabetes Care*. 2008; 31(2):204–209. [PubMed: 18025408]
6. Clark RH, McTaggart JS, Webster R, et al. Muscle dysfunction caused by a KATP channel mutation in neonatal diabetes is neuronal in origin. *Science*. 2010; 329(5990):458–461. [PubMed: 20595581] . Mice with brain-, but not muscle-, specific expression of the V59M mutation in *KCNJ11* have a neuromuscular phenotype similar to patients with this same mutation, suggesting the potential therapeutic importance of blockade of K_{ATP} channels in the brain using sulfonylureas that will cross the blood-brain barrier.
7. Greeley S, Naylor R, Cook L, et al. Creation of the web-based University of Chicago Monogenic Diabetes Registry: using technology to facilitate longitudinal study of rare subtypes of diabetes. *J Diabetes Sci Technol*. 2011; 5(4):879–886. [PubMed: 21880229]
8. Girard CA, Wunderlich FT, Shimomura K, et al. Expression of an activating mutation in the gene encoding the KATP channel subunit Kir6.2 in mouse pancreatic beta cells recapitulates neonatal diabetes. *J Clin Invest*. 2009; 119(1):80–90. [PubMed: 19065048]
9. Remedi MS, Kurata HT, Scott A, et al. Secondary consequences of beta cell inexcitability: identification and prevention in a murine model of K(ATP)-induced neonatal diabetes mellitus. *Cell Metabol*. 2009; 9(2):140–151.
10. Støy J, Edghill EL, Flanagan SE, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc Natl Acad Sci*. 2007; 104(38):15040–15044. [PubMed: 17855560]
11. Edghill EL, Flanagan SE, Patch A-M, 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):1034–1042. [PubMed: 18162506]
12. Polak M, Dechaume A, Cavé 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):1115–1119. [PubMed: 18171712]
13. Molven A, Ringdal M, Nordbø AM, et al. Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. *Diabetes*. 2008; 57(4):1131–1135. [PubMed: 18192540]
14. Colombo C, Porzio O, Liu M, et al. Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. *J Clin Invest*. 2008; 118(6):2148–2156. [PubMed: 18451997]
15. Russo L, Iafusco D, Brescianini S, et al. Permanent diabetes during the first year of life: multiple gene screening in 54 patients. *Diabetologia*. 2011; 54(7):1693–1701. [PubMed: 21544516]

16. Rajan S, Eames SC, Park S-Y, et al. In vitro processing and secretion of mutant insulin proteins that cause permanent neonatal diabetes. *Am J Physiol Endocrinol Metab*. 2010; 298(3):E403–E410. [PubMed: 19952343]
17. Hodish I, Liu M, Rajpal G, et al. Misfolded proinsulin affects bystander proinsulin in neonatal diabetes. *J Biol Chem*. 2010; 285(1):685–694. [PubMed: 19880509]
18. Meur G, Simon A, Harun N, et al. Insulin gene mutations resulting in early-onset diabetes: marked differences in clinical presentation, metabolic status, and pathogenic effect through endoplasmic reticulum retention. *Diabetes*. 2010; 59(3):653–661. [PubMed: 20007936]
19. Park S-Y, Ye H, Steiner DF, Bell GI. Mutant proinsulin proteins associated with neonatal diabetes are retained in the endoplasmic reticulum and not efficiently secreted. *Biochem Biophys Res Commun*. 2010; 391(3):1449–1454. [PubMed: 20034470]
20. Liu M, Haataja L, Wright J, et al. Mutant *INS*-gene induced diabetes of youth: proinsulin cysteine residues impose dominant-negative inhibition on wild-type proinsulin transport. *PLoS ONE*. 2010; 5(10):13333.
21. Hodish I, Absood A, Liu L, et al. In vivo misfolding of proinsulin below the threshold of frank diabetes. *Diabetes*. 2011; 60(8):2092–2101. [PubMed: 21677281]
22. Bonfanti R, Colombo C, Nocerino V, et al. Insulin gene mutations as cause of diabetes in children negative for five type 1 diabetes autoantibodies. *Diabetes Care*. 2009; 32(1):123–125. [PubMed: 18840770]
23. Rubio-Cabezas O, Edghill EL, Argente J, Hattersley AT. Testing for monogenic diabetes among children and adolescents with antibody-negative clinically defined type 1 diabetes. *Diabet Med*. 2009; 26(10):1070–1074. [PubMed: 19900242]
24. Pörksen S, Laborie LB, Nielsen L, et al. Disease progression and search for monogenic diabetes among children with new onset type 1 diabetes negative for ICA, GAD- and IA-2 antibodies. *BMC Endocr Disord*. 2010; 10:16. [PubMed: 20863361]
25. Boesgaard TW, Pruhova S, Andersson EA, et al. Further evidence that mutations in *INS* can be a rare cause of Maturity-Onset Diabetes of the Young (MODY). *BMC Med Genet*. 2010; 11:42. [PubMed: 20226046]
26. Støy J, Steiner DF, Park S-Y, et al. Clinical and molecular genetics of neonatal diabetes due to mutations in the insulin gene. *Rev Endocr Metab Disord*. 2010; 11(3):205–215. [PubMed: 20938745]
27. Garin I, Edghill EL, Akerman I, et al. Recessive mutations in the *INS* gene result in neonatal diabetes through reduced insulin biosynthesis. *Proc Natl Acad Sci*. 2010; 107(7):3105–3110. [PubMed: 20133622]
28. Raile K, O'Connell M, Galler A, et al. Diabetes caused by insulin gene (*INS*) deletion: clinical characteristics of homozygous and heterozygous individuals. *Eur J Endocrinol*. 2011; 165(2):255–60. [PubMed: 21566073]
29. Fendler W, Borowiec M, Antosik K, et al. Paternally inherited proinsulin mutations may result in earlier onset of monogenic diabetes mutation identity effect in monogenic diabetes. *Diabetes Care*. 2011; 34(1):e9. [PubMed: 21193618]
30. Mackay DJG, Temple IK. Transient neonatal diabetes mellitus type 1. *Am J Med Genet C Semin Med Genet*. 2010; 154C(3):335–342. [PubMed: 20803656]
31. Mackay DJG, Callaway JLA, Marks SM, et al. Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in *ZFP57*. *Nat Genet*. 2008; 40(8):949–951. [PubMed: 18622393]
32. Schimmel U. Long-standing sulfonylurea therapy after pubertal relapse of neonatal diabetes in a case of uniparental paternal isodisomy of chromosome 6. *Diabetes Care*. 2009; 32(1):e9. [PubMed: 19114626]
33. Patch AM, Flanagan SE, Boustred C, et al. Mutations in the *ABCC8* gene encoding the SUR1 subunit of the KATP channel cause transient neonatal diabetes, permanent neonatal diabetes or permanent diabetes diagnosed outside the neonatal period. *Diabetes Obes Metab*. 2007; 9 Suppl 2:28–39. [PubMed: 17919176]
34. Vaxillaire M, Dechaume A, Busiah K, et al. New *ABCC8* mutations in relapsing neonatal diabetes and clinical features. *Diabetes*. 2007; 56(6):1737–1741. [PubMed: 17389331]

35. Klupa T, Kowalska I, Wyka K, et al. Mutations in the *ABCC8* (SUR1 subunit of the K(ATP) channel) gene are associated with a variable clinical phenotype. *Clin Endocrinol*. 2009; 71(3):358–62.
36. Gonsorcikova L, Vaxillaire M, Pruhova S, et al. Familial mild hyperglycemia associated with a novel *ABCC8*-V84I mutation within three generations. *Pediatr Diabetes*. 2011; 12(3 Pt 2):266–269. [PubMed: 21214702]
37. Mitchell J, Punthakee Z, Lo B, et al. Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome. *Diabetologia*. 2004; 47(12):2160–2167. [PubMed: 15592663]
38. Chappell L, Gorman S, Campbell F, et al. A further example of a distinctive autosomal recessive syndrome comprising neonatal diabetes mellitus, intestinal atresias and gall bladder agenesis. *Am J Med Genet*. 2008; 146A(13):1713–1717. [PubMed: 18512226]
39. Martinovici D, Ransy V, Vanden Eijnden S, et al. Neonatal hemochromatosis and Martinez-Frias syndrome of intestinal atresia and diabetes mellitus in a consanguineous newborn. *Eur J Med Genet*. 2010; 53(1):25–28. [PubMed: 19887127]
40. Smith SB, Qu H-Q, Taleb N, et al. Rfx6 directs islet formation and insulin production in mice and humans. *Nature*. 2010; 463(7282):775–780. [PubMed: 20148032] . First report of RFX6 mutations as a cause of a previously recognized neonatal diabetes syndrome involving intestinal atresia and gall bladder hypoplasia. It includes a nice combination of mouse and human studies highlighting the importance of this β -cell transcription factor.
41. Poulton CJ, Schot R, Kia SK, et al. Microcephaly with simplified gyration, epilepsy, and infantile diabetes linked to inappropriate apoptosis of neural progenitors. *Am J Hum Genet*. 2011; 89(2): 265–276. [PubMed: 21835305] . Very recent first report of mutations in *IER3IP1* as a new genetic cause of neonatal diabetes involving severe microcephaly.
42. Rubio-Cabezas O, Jensen JN, Hodgson MI, et al. Permanent neonatal diabetes and enteric anendocrinosis associated with biallelic mutations in *NEUROG3*. *Diabetes*. 2011; 60(4):1349–1353. [PubMed: 21378176] . Represents one of the first reports of rare cases of neonatal diabetes with severe congenital diarrhea caused by *NEUROG3* mutations. The lack of pancreatic exocrine insufficiency and study of gut pathology demonstrate that the β -cell transcription factor *NEUROG3* is also critical for enteroendocrine cellular development..
43. Pinney SE, Oliver-Krasinski J, Ernst L, et al. Neonatal diabetes and congenital malabsorptive diarrhea attributable to a novel mutation in the human neurogenin-3 gene coding sequence. *J Clin Endocrinol Metab*. 2011; 96(7):1960–1965. [PubMed: 21490072] . Represents one of the first reports of rare cases neonatal diabetes with severe congenital diarrhea caused by *NEUROG3* mutations. The lack of pancreatic exocrine insufficiency and study of gut pathology demonstrate that the β -cell transcription factor *NEUROG3* is also critical for enteroendocrine cellular development..
44. Wang J, Cortina G, Wu SV, et al. Mutant neurogenin-3 in congenital malabsorptive diarrhea. *N Engl J Med*. 2006; 355(3):270–280. [PubMed: 16855267]
45. Malecki MT, Jhala US, Antonellis A, et al. Mutations in *NEUROD1* are associated with the development of type 2 diabetes mellitus. *Nat Genet*. 1999; 23(3):323–328. [PubMed: 10545951]
46. Rubio-Cabezas O, Minton JAL, Kantor I, et al. Homozygous mutations in *NEUROD1* are responsible for a novel syndrome of permanent neonatal diabetes and neurological abnormalities. *Diabetes*. 2010; 59(9):2326–2331. [PubMed: 20573748] . First description of rare cases of neonatal diabetes caused by the *MODY* gene *NEUROD1*. Patients demonstrate a severe neurologic phenotype including cerebellar hypoplasia but interestingly do not exhibit pancreatic exocrine deficiency.
47. Sellick GS, Barker KT, Stolte-Dijkstra I, et al. Mutations in *PTF1A* cause pancreatic and cerebellar agenesis. *Nat Genet*. 2004; 36(12):1301–1305. [PubMed: 15543146]
48. Hoveyda N, Shield JP, Garrett C, et al. Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of a new recessive syndrome. *J Med Genet*. 1999; 36(9):700–704. [PubMed: 10507728]
49. Tutak E, Satar M, Yapicioğlu H, et al. A Turkish newborn infant with cerebellar agenesis/neonatal diabetes mellitus and *PTF1A* mutation. *Genet Couns*. 2009; 20(2):147–152. [PubMed: 19650412]

50. Senée V, Chelala C, Duchatelet S, et al. Mutations in *GLIS3* are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. *Nat Genet.* 2006; 38(6):682–687. [PubMed: 16715098]
51. Kang HS, Beak JY, Kim Y-S, et al. Glis3 is associated with primary cilia and *Wwtr1/TAZ* and implicated in polycystic kidney disease. *Mol Cell Biol.* 2009; 29(10):2556–2569. [PubMed: 19273592]
52. Watanabe N, Hiramatsu K, Miyamoto R, et al. A murine model of neonatal diabetes mellitus in *Glis3*-deficient mice. *FEBS Lett.* 2009; 583(12):2108–2113. [PubMed: 19481545]
53. Dimitri P, Warner JT, Minton JAL, et al. Novel *GLIS3* mutations demonstrate an extended multisystem phenotype. *Eur J Endocrinol.* 2011; 164(3):437–443. [PubMed: 21139041]
54. Stoffers DA, Zinkin NT, Stanojevic V, et al. Pancreatic agenesis attributable to a single nucleotide deletion in the human *IPF1* gene coding sequence. *Nat Genet.* 1997; 15(1):106–110. [PubMed: 8988180]
55. Stoffers DA, Ferrer J, Clarke WL, Habener JF. Early-onset type-II diabetes mellitus (MODY4) linked to *IPF1*. *Nat Genet.* 1997; 17(2):138–139. [PubMed: 9326926]
56. Wright NM, Metzger DL, Borowitz SM, Clarke WL. Permanent neonatal diabetes mellitus and pancreatic exocrine insufficiency resulting from congenital pancreatic agenesis. *Am J Dis Child.* 1993; 147(6):607–609. [PubMed: 8506821]
57. Thomas IH, Saini NK, Adhikari A, et al. Neonatal diabetes mellitus with pancreatic agenesis in an infant with homozygous *IPF-1* Pro63fsX60 mutation. *Pediatr Diabetes.* 2009; 10(7):492–496. [PubMed: 19496967]
58. Fajans SS, Bell GI, Paz VP, et al. Obesity and hyperinsulinemia in a family with pancreatic agenesis and MODY caused by the *IPF1* mutation Pro63fsX60. *Transl Res.* 2010; 156(1):7–14. [PubMed: 20621032]
59. Schwitzgebel VM, Mamin A, Brun T, et al. Agenesis of human pancreas due to decreased half-life of insulin promoter factor 1. *J Clin Endocrinol Metab.* 2003; 88(9):4398–4406. [PubMed: 12970316]
60. Nicolino M, Claiborn KC, Senée V, et al. A novel hypomorphic *PDX1* mutation responsible for permanent neonatal diabetes with subclinical exocrine deficiency. *Diabetes.* 2010; 59(3):733–740. [PubMed: 20009086] . First report of *PDX1* mutations causing neonatal diabetes in which the patients did not exhibit clinical pancreatic exocrine insufficiency and the pancreas was present but hypoplastic.
61. Edghill EL, Khamis A, Weedon MN, et al. Sequencing *PDX1* (insulin promoter factor 1) in 1788 UK individuals found 5% had a low frequency coding variant, but these variants are not associated with type 2 diabetes. *Diabet Med.* 2011; 28(6):681–684. [PubMed: 21569088] . Important demonstration that low-frequency variants in *PDX1* are not associated with adult-onset diabetes, thus suggesting that *PDX1* mutations are a very rare cause of MODY. Similar studies will be needed to better establish causality of mutations in other genes that have been implicated as a cause of MODY, including neonatal diabetes genes in which many heterozygous relatives exhibit diabetes.
62. Yorifuji T, Kurokawa K, Mamada M, et al. Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: phenotyp-ically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. *J Clin Endocrinol Metab.* 2004; 89(6):2905–2908. [PubMed: 15181075]
63. Edghill EL, Bingham C, Slingerland AS, 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):1301–1306. [PubMed: 17116179]
64. Haldorsen IS, Vesterhus M, Raeder H, et al. Lack of pancreatic body and tail in *HNF1B* mutation carriers. *Diabet Med.* 2008; 25(7):782–787. [PubMed: 18644064]
65. Yasuda T, Kajimoto Y, Fujitani Y, et al. *PAX6* mutation as a genetic factor common to aniridia and glucose intolerance. *Diabetes.* 2002; 51(1):224–230. [PubMed: 11756345]
66. Wen JH, Chen YY, Song SJ, et al. Paired box 6 (*PAX6*) regulates glucose metabolism via proinsulin processing mediated by prohormone convertase 1/3 (*PC1/3*). *Diabetologia.* 2009; 52(3):504–513. [PubMed: 19034419]

67. Solomon BD, Pineda-Alvarez DE, Balog JZ, et al. Compound heterozygosity for mutations in *PAX6* in a patient with complex brain anomaly, neonatal diabetes mellitus, and microphthalmia. *Am J Med Genet.* 2009; 149A(11):2543–2546. [PubMed: 19876904]
68. Inoue H, Tanizawa Y, Wasson J, 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): 143–148. [PubMed: 9771706]
69. Rigoli L, Lombardo F, Di Bella C. Wolfram syndrome and *WFS1* gene. *Clin Genet.* 2011; 79(2): 103–117. [PubMed: 20738327]
70. Riggs AC, Bernal-Mizrachi E, Ohsugi M, et al. Mice conditionally lacking the Wolfram gene in pancreatic islet beta cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis. *Diabetologia.* 2005; 48(11):2313–2321. [PubMed: 16215705]
71. Fonseca SG, Ishigaki S, Oslowski CM, et al. Wolfram syndrome 1 gene negatively regulates ER stress signaling in rodent and human cells. *J Clin Invest.* 2010; 120(3):744–755. [PubMed: 20160352]
72. Cryns K, Sivakumaran TA, van den Ouweland JMW, et al. Mutational spectrum of the *WFS1* gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. *Hum Mutat.* 2003; 22(4):275–287. [PubMed: 12955714]
73. Rendtorff ND, Lodahl M, Boulahbel H, et al. Identification of p. A684V missense mutation in the *WFS1* gene as a frequent cause of autosomal dominant optic atrophy and hearing impairment. *Am J Med Genet.* 2011; 155A(6):1298–1313. [PubMed: 21538838]
74. Barrett TG, Bunday SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet.* 1995; 346(8988):1458–1463. [PubMed: 7490992]
75. Rohayem J, Ehlers C, Wiedemann B, et al. Diabetes and neurodegeneration in Wolfram syndrome: a multicenter study of phenotype and genotype. *Diabetes Care.* 2011; 34(7):1503–1510. [PubMed: 21602428]
76. Bergmann AK, Sahai I, Falcone JF, et al. Thiamine-responsive megaloblastic anemia: identification of novel compound heterozygotes and mutation update. *J Pediatr.* 2009; 155(6):888–892. e1. [PubMed: 19643445]
77. Yeşilkaya E, Bideci A, Temizkan M, et al. A novel mutation in the *SLC19A2* gene in a Turkish female with thiamine-responsive megaloblastic anemia syndrome. *J Trop Pediatr.* 2009; 55(4): 265–267. [PubMed: 18614593]
78. Ayca Z, Baş VN, Cetinkaya S, et al. Thiamine-responsive megaloblastic anemia syndrome with atrial standstill: a case report. *J Pediatr Hematol Oncol.* 2011; 33(2):144–147. [PubMed: 21285901]
79. Lagarde WH, Underwood LE, Moats-Staats BM, Calikoglu AS. Novel mutation in the *SLC19A2* gene in an African-American female with thiamine-responsive megaloblastic anemia syndrome. *Am J Med Genet.* 2004; 125A(3):299–305. [PubMed: 14994241]
80. Onal H, Bariş S, Ozdil M, et al. Thiamine-responsive megaloblastic anemia: early diagnosis may be effective in preventing deafness. *Turk J Pediatr.* 2009; 51(3):301–304. [PubMed: 19817279]
81. Santer R, Schneppenheim R, Dombrowski A, et al. Mutations in *GLUT2*, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. *Nat Genet.* 1997; 17(3):324–326. [PubMed: 9354798]
82. Santer R, Schneppenheim R, Suter D, et al. Fanconi-Bickel syndrome—the original patient and his natural history, historical steps leading to the primary defect, and a review of the literature. *Eur J Pediatr.* 1998; 157(10):783–797. [PubMed: 9809815]
83. Santer R, Groth S, Kinner M, et al. The mutation spectrum of the facilitative glucose transporter gene *SLC2A2 (GLUT2)* in patients with Fanconi-Bickel syndrome. *Hum Genet.* 2002; 110(1):21–29. [PubMed: 11810292]
84. Taha D, Al-Harbi N, Al-Sabban E. Hyperglycemia and hypo-insulinemia in patients with Fanconi-Bickel syndrome. *J Pediatr Endocrinol Metab.* 2008; 21(6):581–586. [PubMed: 18717244]
85. Yoo HW, Shin Y-L, Seo E-J, Kim GH. Identification of a novel mutation in the *GLUT2* gene in a patient with Fanconi-Bickel syndrome presenting with neonatal diabetes mellitus and galactosaemia. *Eur J Pediatr.* 2002; 161(6):351–353. [PubMed: 12029458]

86. Manz F, Bickel H, Brodehl J, et al. Fanconi-Bickel syndrome. *Pediatr Nephrol.* 1987; 1(3):509–518. [PubMed: 3153325]
87. Müller D, Santer R, Krawinkel M, et al. Fanconi-Bickel syndrome presenting in neonatal screening for galactosaemia. *J Inher Metab Dis.* 1997; 20(4):607–608. [PubMed: 9266402]
88. Rubio-Cabezas O, Minton JAL, Caswell R, et al. Clinical heterogeneity in patients with *FOXP3* mutations presenting with permanent neonatal diabetes. *Diabetes Care.* 2009; 32(1):111–116. [PubMed: 18931102]
89. Wolcott CD, Rallison ML. Infancy-onset diabetes mellitus and multiple epiphyseal dysplasia. *J Pediatr.* 1972; 80(2):292–297. [PubMed: 5008828]
90. Delépine M, Nicolino M, Barrett T, et al. *EIF2AK3*, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat Genet.* 2000; 25(4):406–409. [PubMed: 10932183]
91. Gupta S, McGrath B, Cavener DR. PERK (EIF2AK3) regulates proinsulin trafficking and quality control in the secretory pathway. *Diabetes.* 2010; 59(8):1937–1947. [PubMed: 20530744]
92. Ozbek MN, Senée V, Aydemir S, et al. Wolcott-Rallison syndrome due to the same mutation (W522X) in *EIF2AK3* in two unrelated families and review of the literature. *Pediatr Diabetes.* 2010; 11(4):279–285. [PubMed: 20202148]
93. Rubio-Cabezas O, Patch A-M, Minton JAL, et al. Wolcott-Rallison syndrome is the most common genetic cause of permanent neonatal diabetes in consanguineous families. *J Clin Endocrinol Metab.* 2009; 94(11):4162–4170. [PubMed: 19837917]
94. Njolstad PR, Sovik O, Cuesta-Munoz A, et al. Neonatal diabetes mellitus due to complete glucokinase deficiency. *N Engl J Med.* 2001; 344(21):1588–1592. [PubMed: 11372010]
95. Borowiec M, Mysliwiec M, Fendler W, et al. Phenotype variability and neonatal diabetes in a large family with heterozygous mutation of the glucokinase gene. *Acta Diabetol.* 2011; 48(3):203–208. [PubMed: 21437567]
96. Bakri D, Gershoni-Baruch R, Shehadeh N. Permanent neonatal diabetes. *Isr Med Assoc J.* 2004; 6(5):290–291. [PubMed: 15151370]
97. Turkkahraman D, Bircan I, Tribble ND, et al. Permanent neonatal diabetes mellitus caused by a novel homozygous (T168A) glucokinase (*GCK*) mutation: initial response to oral sulphonylurea therapy. *J Pediatr.* 2008; 153(1):122–126. [PubMed: 18571549]
98. Bennett K, James C, Mutair A, et al. Four novel cases of permanent neonatal diabetes mellitus caused by homozygous mutations in the glucokinase gene. *Pediatr Diabetes.* 2011; 12(3 Pt 1):192–196. [PubMed: 21518409]
99. Greeley SAW, John PM, Winn AN, et al. The cost-effectiveness of personalized genetic medicine: the case of genetic testing in neonatal diabetes. *Diabetes Care.* 2011; 34(3):622–627. [PubMed: 21273495] . This rare example of the realization of personalized medicine reports that genetic testing in neonatal diabetes allows not only for better treatment outcome, but does so at significant cost savings. Such studies will be critical in informing the expansion of genetic testing to patients diagnosed at older ages, including testing *MODY* genes in those with suspected adult-onset monogenic diabetes.
100. Mohamadi A, Clark L, Lipkin P, 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.* 2009; 11(3):203–207. [PubMed: 19686306]
101. Gach A, Wyka K, Malecki MT, et al. Islet-specific antibody seroconversion in patients with long duration of permanent neonatal diabetes caused by mutations in the *KCNJ11* gene. *Diabetes Care.* 2007; 30(8):2080–2082. [PubMed: 17475937]
102. Bonnefond A, Durand E, Sand O, et al. Molecular diagnosis of neonatal diabetes mellitus using next-generation sequencing of the whole exome. *PLoS ONE.* 2010; 5(10):e13630. [PubMed: 21049026] . This study demonstrates what will surely be the future direction of genetic testing, especially for Mendelian disorders such as neonatal diabetes that have many possible causes, including presumed unknown genes.

Table 1

Monogenic causes of congenital diabetes known to occur within the first year of life

Gene	Protein/function	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas appearance/ exocrine function	Other features	References
<i>PLAGL1</i> <i>HYMAI</i> (6q24)	Overexpression of paternally expressed genes <i>PLAGL1</i> (zinc finger protein or ZAC tumor suppressor) and <i>HYMAI</i> (non-protein coding) within the imprinted region of chromosome 6q24/unknown function	TNDM	UPD6 (40%); de novo, nonrecurrent, paternal duplication (40%, may be inherited) or maternal methylation defect (20%); autosomal recessive; e.g., <i>ZFP57</i>	Within days; remission within months; relapse during adolescence	Normal/normal	Very SGA; macroglossia and/or umbilical hernia often present; other features may be seen in those with HIL, especially <i>ZFP57</i> mutations (see below)	[30]
<i>ZFP57</i>	Zinc finger protein 57/transcription factor with a role in maintenance of imprinted DNA methylation	TNDM	Autosomal recessive	Similar to 6q24	Normal/normal	Very SGA; HIL (9/9); macroglossia (6/9); variable developmental delay (6/9); umbilical defect (3/9); CHD (3/9); visual impairment (3/9); epilepsy (2/9)	[31]
<i>KCNJ11</i>	Inward rectifier K(+) channel (Kir6.2) subunit of K_{ATP}	PNDM (more often) or TNDM (less often); DEND	Spontaneous (80%) or autosomal dominant	<6 months; rarely later	Normal/normal	Often SGA; possible developmental delay; usually responsive to sulfonylurea therapy	[1–3]
<i>ABCC8</i>	Sulfonylurea receptor 1 (SUR1) subunit of K_{ATP}	PNDM (less often) or TNDM (more often); DEND	Spontaneous (80%) or autosomal dominant	<6 months; rarely later	Normal/normal	Often SGA; usually responsive to sulfonylurea therapy	[3, 5]
<i>INS</i>	Insulin/hormone	PNDM (more often) or TNDM (rarely)	Spontaneous (80%), autosomal dominant or recessive (rarely)	<6 months; less often later	Normal/normal	Often SGA; rare later-onset patients with a MODY or antibody-negative phenotype	[10–15, 22–25, 27, 28]
<i>EIF2AK3</i>	Eukaryotic translation initiation factor 2- α kinase 3 (EIF2AK3)/kinase involved in regulation of translation	Wolcott-Rallison syndrome (WRS)	Autosomal recessive	Most cases: within weeks (2–28 weeks); 1 case: 30 months	Rare hypoplasia/often reduced (25%)	Mild SGA or normal, rarely very SGA; epiphyseal dysplasia (90% to 100%); acute liver failure (60% to 75%); developmental delay (60% to 80%); hypothyroidism (~ 25%); exocrine pancreatic dysfunction (~ 25%)	[89, 90, 92, 93]
<i>FOXP3</i>	Forkhead box protein P3 (FoxP3)/transcription factor	Immunodysregulation polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	X-linked recessive	Days–3.5 months	Normal/normal	Only males affected; severe immune dysregulation; chronic diarrhea with villus atrophy (95%); pancreatic and thyroid autoantibodies (75%); thyroiditis (20%); eczema (50%); anemia (30%); often die before 1 year	[88]
<i>GCK</i>	Glucokinase/glycolytic enzyme	PNDM; MODY2	Autosomal recessive (PNDM), or autosomal	PNDM: days of life; MODY2:	Normal/normal	PNDM: very SGA, 12/14 homozygous, 1/14 compound	[94–98]

Gene	Protein/function	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas appearance/ exocrine function	Other features	References
			dominant (MODY2)	present from birth but not usually detected until later		heterozygous, 1/14 heterozygous (unclear mechanism), parents have impaired fasting glucose with <i>GCK</i> -MODY (MODY2)	
<i>PDX1</i>	Pancreas/duodenum homeobox protein 1 (PDX1 or IPF1)/ transcription factor	PNDM with pancreatic agenesis/ hypoplasia	Autosomal recessive	3/5 cases: within days; 2/5 cases: 12–15 days	Absent (1/5), small (3/5) or normal (1/5)/absent (3/5) or reduced (2/5)	SGA; diarrhea; malnutrition; parents have <i>PDX1</i> MODY (MODY4)	[54–59, 60•, 61•]
<i>PTF1A</i>	Pancreas transcription factor 1, subunit α (PTF1A)/bHLH transcription factor	PNDM with cerebellar and pancreatic agenesis	Autosomal recessive	5 cases: within days	Absent/ absent	Very SGA; cerebellar agenesis; flexion contractures; poor subcutaneous fat; optic nerve hypoplasia; detectable C-peptide/insulin	[47–49]
<i>NEUROD1</i>	(NeuroD1 or BETA2)/bHLH transcription factor	PNDM with cerebellar (but not pancreatic) hypoplasia	Autosomal recessive	2 cases; by 2 months	Normal/ normal	SGA; severe cerebellar hypoplasia; moderate to severe developmental delay; sensorineural deafness; visual impairment	[46•]
<i>NEUROG3</i>	(NeuroG3 or NGN3)/bHLH transcription factor	PNDM with severe congenital diarrhea	Autosomal recessive	2/5 cases: within days; 2/5 cases: by 9 years	Small/4/5 normal	Very SGA; severe intractable congenital diarrhea unresponsive to pancreatic enzyme replacement with absent intestinal enteroendocrine cells	[42•, 43•, 44]
<i>RFX6</i>	DNA-binding protein (RFX6)/ winged-helix transcription factor	PNDM with intestinal atresia, gall bladder hypoplasia	Autosomal recessive	5 cases: within days	Small/ normal	Very SGA; intestinal atresias; gall bladder hypoplasia/aplasia; diarrhea	[37–39, 40•]
<i>IER3IP1</i>	Immediate early response 3 interacting protein 1 (IER3IP1)	PNDM with microcephaly	Autosomal recessive	2 cases: birth- 2 months	Normal/ normal	Microcephaly with simplified gyral pattern; severe infantile epileptic encephalopathy	[41•]
<i>HNF1B</i>	Hepatocyte nuclear factor 1 β (HNF-1 β)/transcription factor	TNDM/PNDM; (RCAD; MODY5)	Spontaneous or autosomal dominant	2 cases: 15- 17 days	Hypoplastic/ reduced	Very SGA; renal abnormalities; relapsing/remitting DM (RCAD; renal cysts, urogenital abnormalities)	[62, 63]
<i>GLIS3</i>	Glioma-associated oncogene-similar family zinc finger 3 (GLIS3)/ Krippel-like transcription factor	Neonatal diabetes with congenital hypothyroidism (NDH)	Autosomal recessive	8 cases: within days	Small, normal or cystic/ normal or reduced (2/8)	SGA; congenital primary hypothyroidism; glaucoma (4/8); liver fibrosis (5/8); cystic kidney disease (4/8); osteopenia (1/8); deafness (1/8)	[50, 53]
<i>PAX6</i>	Paired box 6/paired box and homeo domain box containing transcription factor	PNDM with severe microcephaly and eye defects	Autosomal recessive	2 brothers: within days (other case: DM not	Normal/not reported	Brain malformations; microcephaly; microphthalmia (eye defects in parents); panhypopituitarism	[65–67]

Gene	Protein/function	Phenotypes/ syndromes	Inheritance	Age of diabetes onset	Pancreas appearance/ exocrine function	Other features	References
<i>WFS1</i>	Wolframin/membrane glycoprotein	Wolfram syndrome; DIDMOAD	Autosomal recessive	Median 6 years (3 weeks– 14 years)	Normal/ normal	Optic atrophy (earliest feature); diabetes insipidus; deafness	[68, 69, 74, 75]
<i>SLC19A2</i>	Thiamine transporter 1/transport thiamine across the plasma membrane	TRMA syndrome	Autosomal recessive	12 cases: 2– 13 months; Others: DM later	Normal/ normal	TRMA; sensorineural deafness; occasional CHD (conduction defects); short stature	[76–80]
<i>SLC2A2</i>	GLUT2/facilitative glucose transporter	Fanconi-Bickel syndrome (FBS)	Autosomal recessive	1 case: 6 days; Others: IGT or DM in infancy/ childhood	Normal/ normal	Hepatomegaly related to hepatorenal glycogen accumulation; proximal tubular nephropathy with glucosuria and hypophosphatemic rickets; glucose intolerance or diabetes; galactosemia	[81–87]

bHLH basic helix-loop-helix; *CHD* congenital heart defect; *DEND* developmental delay, epilepsy, neonatal diabetes; *DIDMOAD* diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; *DM* diabetes mellitus; *HIL* hypomethylation of multiple imprinted loci; *IGT* impaired glucose tolerance; *KATP* ATP-sensitive potassium channel; *MODY* maturity-onset diabetes of the young; *PNDM* permanent neonatal diabetes; *RCAD* renal cysts and diabetes; *SGA* small for gestational age; *TNDM* transient neonatal diabetes; *TRMA* thiamine-responsive megaloblastic anemia

Table 2

Clinical features associated with multiple monogenic causes of neonatal diabetes

Clinical feature	Genes to consider testing
Neurodevelopmental disability	<i>KCNJ11, ABCC8, EIF2AK3, GLIS3, NEUROD1, PTF1A, PAX6, IER3IP1</i>
Diarrhea and/or exocrine pancreatic insufficiency	<i>NEUROG3, FOXP3, PDX1, PTF1A, RFX6, GLIS3</i>
Thyroid dysfunction	<i>GLIS3, FOXP3, EIF2AK3</i>
Transient or relapsing/remitting diabetes	6q24 abnormalities, <i>ZFP57, KCNJ11, ABCC8, INS, HNF1B, SLC2A2, SLC19A2</i>
Family history of diabetes	Both parents or in their families: <i>GCK, PDX1, NEUROD1, PTF1A, RFX6, WFS1, INS</i> (recessive mutations upstream of coding region or deletions) One parent (neonatal or adult onset): <i>ABCC8, KCNJ11, INS, HNF1B, GCK</i> , 6q24 duplications (paternally inherited)
Kidney structural or functional defects	<i>HNF1B</i> (structural anomalies and/or cysts), <i>GLIS3</i> (cysts), <i>EIF2AK3</i> (acute renal failure), <i>SLC2A2</i> (tubular dysfunction with glucosuria and phosphaturia)
Liver dysfunction	<i>EIF2AK3</i> (episodic liver failure), <i>SLC2A2</i> (hepatomegaly without liver failure), <i>RFX6</i> (gall bladder hypoplasia with intestinal atresia and malformations), <i>GLIS3</i> (liver fibrosis in some cases)
Skeletal abnormalities	<i>EIF2AK3</i> (epiphyseal dysplasia will be apparent radiographically if not clinically), <i>GLIS3</i> (osteopenia with elevated alkaline phosphatase)
Visual impairment	<i>PAX6</i> (aniridia, microphthalmia, also in parents), <i>NEUROD1, WFS1</i> (optic atrophy outside neonatal period), <i>PTF1A</i> (optic nerve hypoplasia), <i>GLIS3</i> (congenital glaucoma)
Deafness	<i>WS1, SLC19A2, NEUROD1, GLIS3</i>
Megaloblastic anemia	<i>SLC19A2</i>