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Congenital Diabetes: Comprehensive Genetic Testing Allows for Improved Diagnosis and Treatment of Diabetes and Other Associated Features

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Abstract

Purpose of Review—The goal of this review is to provide updates on congenital (neonatal) diabetes from 2011 to present, with an emphasis on publications from 2015 to present.

Recent Findings—There has been continued worldwide progress in uncovering the genetic causes of diabetes presenting within the first year of life, including the recognition of nine new causes since 2011. Management has continued to be refined based on underlying molecular cause, and longer-term experience has provided better understanding of the effectiveness, safety, and sustainability of treatment. Associated conditions have been further clarified, such as neurodevelopmental delays and pancreatic insufficiency, including a better appreciation for how these “secondary” conditions impact quality of life for patients and their families.

Summary—While continued research is essential to understand all forms of congenital diabetes, these cases remain a compelling example of personalized genetic medicine.

Keywords

Neonatal diabetes; Congenital diabetes; Monogenic diabetes; NDM; PNDM; TNDM

Introduction

Diabetes is an etiologically heterogeneous disorder that includes both polygenic and monogenic forms. Monogenic diabetes includes Maturity-Onset Diabetes of the Young (MODY), syndromic diabetes, and monogenic diabetes diagnosed during infancy—often called *neonatal diabetes*—which will be the focus of this review. Traditionally, *neonatal diabetes* has been defined as a patient diagnosed under 6 months of age. Since these cases are often diagnosed with diabetes after 1 month of age (outside of the true neonatal period), and may be diagnosed between 6 and 12 months of age, we prefer the term *congenital*

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

diabetes to define monogenic forms of diabetes diagnosed under 1 year of age. This emphasizes the genetic nature of this group of disorders rather than the age of onset, and we will use this terminology throughout this review. Congenital forms of diabetes are diverse and can include both permanent and transient phenotypes, as well as include or lack co-occurring conditions. Healthcare providers have become increasingly aware of these genetic conditions, and thus, research and knowledge has subsequently expanded. This review will build upon a previously published version by our team [1] and will focus on updates to the congenital diabetes field since 2011, with particular emphasis on clinical and genetic updates in the last 2 to 3 years.

Genes known to be associated with congenital forms of diabetes are noted in Table 1. A summary of pertinent clinical features are noted in Table 2.

KCNJ11/ABCC8: Congenital Diabetes Due to Activating Mutations of the KATP Channel

Although variable, based on country, diagnosis age, and possible consanguinity, the incidence of congenital diabetes is estimated to be about 1 out of every 100,000 births [78, 79, 80••, 81, 82]. Activating mutations in either *KCNJ11* or *ABCC8* remain the most common cause of permanent congenital diabetes, together accounting for almost 50% of cases, and can usually be well managed with oral sulfonylurea pills instead of insulin injections [1, 10]. Transition from insulin to sulfonylureas can be successfully accomplished in both an inpatient and outpatient setting with published guidelines [10], depending on the comfort of the family and healthcare team. Seeking advice from recognized centers with extensive experience is still recommended (monogenicdiabetes.org, diabetesgenes.org). Progress has been made toward answering many of the most common questions about treatment and prognosis for patients with *KCNJ11* or *ABCC8*-related diabetes:

> How sustainable will treatment with oral sulfonylureas be, and will age, obesity or other factors eventually require supplemental insulin or other medications?

The age at which sulfonylureas are initiated may have a significant impact on clinical outcomes, as supported by a study of 58 participants with *KCNJ11*-related diabetes [11•]. This study found a significant decrease in HbA1c after transition (8.5 to 6.2%, $p < 0.001$) and a correlation between the age that sulfonylureas were started and dose required at the time of study analysis ($r = 0.8$, $p < 0.001$). Although some participants did require the addition of other medications, they were all transitioned in adolescence or later (≥ 13 years old), further emphasizing the need for early initiation of sulfonylureas in these patients. A separate study of 81 participants with *KCNJ11* mutations found that 93% were able to maintain good glycemic control (median HbA1c 6.4% at follow-up) on sulfonylureas with a median follow-up duration of 10 years [83]. The mutation subtype may also affect the ability to successfully transition, as noted in a study of 127 participants with *KCNJ11*-related diabetes [12]. Those who were able to transition (88% of participants) experienced a significant decrease in HbA1c (8.2 to 5.9%, $p = 0.001$). In vitro studies showed that KATP channels with mutations of those who were unable to transition had a significantly lower tolbutamide block percentage (< 63%), as compared to > 73% of mutations who were

(mostly) responsive to sulfonylureas. Duration of diabetes was also a predictor of successful transfer. Patients with these mutations may require up to 2.0 mg/kg/day, and thus glycemic control must continue to be monitored and medical adherence should be promoted, given the potentially large number of pills required. Due to the potential neuroprotective effects, we recommend continuing sulfonylurea therapy even when additional medications are required. In the University of Chicago Monogenic Diabetes Registry, some patients have shown benefit with the additional of other oral agents, such as dipepdidyl-peptidase-IV inhibitors [13], or newer injectable medications such as glucagon-like peptide-1 receptor agonists (unpublished). Other factors, such as nutrition and exercise, may also impact HbA1c in these patients. Continued longitudinal follow-up of large cohorts of patients with these mutations will be essential to fully understanding the safety and efficacy of sulfonylureas. Randomized controlled trials could be useful in allowing for clearer findings regarding the addition of medications other than sulfonylureas.

> 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?

A recent study from our Monogenic Diabetes Registry sought to address how frequently hypoglycemia occurs in patients with *KCNJ11*-related congenital diabetes [14••]. We collected subject- or caregiver-reported survey data (n =30), as well as continuous glucose monitoring data (available for seven participants). The cohort was fairly young; mean age at the time of survey completion was 10.2 years (median 8 years, IQR 5.25–12.75 years). Most were diagnosed during the first 6 months of life (median 0.15 years, IQR 0.09–0.29 years), and all were taking sulfonylureas (median dose 0.39 mg/kg/day, IQR 0.24–0.88 mg/kg/day). Overall, their most recent HbA1c were in target range (median: 5.7%, IQR 5.5–6.1%). Mild to moderate hypoglycemia (“conscious and mostly able to help themselves”) occurred infrequently, with 89% reporting mild-moderate occurrences once a month or less. No episodes of severe hypoglycemia (“seizure of loss of consciousness”) were reported. There was no association between sulfonylurea dose and frequency of hypoglycemia, which may be reassuring to healthcare providers as these patients may require doses up to 2.0 mg/kg/day. A separate study confirmed these findings; out of 81 patients with *KCNJ11* mutations, no episodes of severe hypoglycemia were reported over 809 patient-years on sulfonylureas [83].

> To what extent will neurodevelopmental effects be improved or even prevented by sulfonylurea treatment?

One study utilized the Beery-Buktenica Developmental Test of Visual-Motor Integration to test 19 participants with *KCNJ11* mutations with and without neurodevelopmental delay (R201H: 8, V59M or V59A: 8, R201C: 1, Y330C: 1, E322K: 1) [15]. All children with R201H performed in the “normal” range, while participants with V59M or V59A mutations scored the lowest. Although all participants were on sulfonylureas at the time of assessment, the age at which the participant was started on a sulfonylurea was inversely correlated with scores on the visuomotor assessment ($p < 0.05$). Although certain KATP mutations have consistently been reported to be associated with significant developmental delay and/or seizures termed DEND (developmental delay, epilepsy, neonatal diabetes), it has not been

clear whether those without obvious developmental delay may in fact have more mild neurodevelopmental and/or behavioral challenges. A study of *KCNJ11* patients (n =23) and their unaffected siblings (n = 20) revealed that even patients with more mild *KCNJ11* mutations ("without global developmental delay") had significant differences in performance on standardized tests compared to their siblings [16•]. These differences were present in areas such as IQ, academic achievement, and executive function, while those patients with global developmental delay also exhibited differences in social awareness and behavior. These findings were supported by a separate study of ten patients with *KCNJ11*-related congenital diabetes and seven unaffected sibling controls [17]. In addition to neurodevelopmental delays, patients with *KCNJ11* mutations were significantly more likely than their sibling controls to be diagnosed with ADHD (43 vs. 8%, p <0.05) and to have sleep difficulties (p <0.01) [18]. Psychiatric disorders, such as anxiety and autism, were identified frequently in a separate research study [19•]. However, most of these disorders had not been clinically identified prior to that study, emphasizing the importance of screening children with *KCNJ11*-related diabetes for a variety of neuropsychiatric conditions.

In regard to improvement with sulfonylurea treatment, one study followed 19 participants during their transition from insulin to sulfonylureas [20•].MRIs, nerve and muscle testing, and neurodevelopmental assessments were performed at baseline and 6–12 months following the transition. Sulfonylurea use correlated with improvements in neuropsychomotor measures as well as with improved glycemic control. Studies using a mouse model have suggested that sulfonylureas may have a limited ability to affect channel function within the brain [21•]. Further research is needed to fully understand the effect that sulfonylureas may have on neurodevelopment and to what extent any benefit may relate to dose, drug choice, and/or age of treatment initiation.

> How is quality of life of these patients and their families affected? What are their biggest concerns in relation to this condition?

A discussion group for families with *KCNJ11*- or *ABCC8*-related diabetes was formed in April 2010 through the University of Chicago Monogenic Diabetes Registry. Over 5 years, the group grew to consist of 64 participants (patients or caregivers) and 11 researchers, and over 1400 messages were sent by 2015 [84]. Qualitative analysis revealed that both informational support (44% of messages) and psychosocial/emotional support (31.4% of messages) were common requests. In terms of topics discussed, neurodevelopmental concerns (472 messages) were nearly as popular as diabetes treatments (503 messages), emphasizing the impact that these associated conditions can have on patients and their families. This study highlights the importance of providing an opportunity for social support and knowledge transfer for rare conditions such as these.

Such questions and many others continue to be addressed through international efforts, such as the University of Chicago Monogenic Diabetes Registry (http://monogenicdiabetes.org), to track long-term outcomes in as many patients as possible [85]. Over 1500 families with atypical diabetes from around the world are now included within our Registry, including over 150 participants who have mutations in *KCNJ11* or *ABCC8*.

INS: Diabetes Caused by Mutations in the Insulin Gene

The second most common cause of permanent congenital diabetes is mutations in the insulin gene (*INS*) [1, 22]. The most common mutations are autosomal dominantly inherited heterozygous missense mutations that generate improperly folded proteins which are likely held in the endoplasmic reticulum, leading to beta-cell stress, and eventually beta-cell death [23]. A recent case of a novel homozygous intronic mutation describes a different mechanism of action via a mutated translational product without beta-cell death [24]. While most mutations in the *INS* gene cause diabetes onset within the first year of life, certain mutations can cause a more mild dysfunction with later diabetes onset and a more MODY-like phenotype [25]. Infancy-onset cases will require lifelong exogenous insulin therapy, while patients with INS-MODY may respond well to insulin and other anti-hyperglycemic agents. The use of sulfonylureas is not recommended due to the reduced beta-cell mass that is likely present in these cases. A recent case study suggests that initiating intensive insulin therapy at the first sign of mild glycemic irregularities may help to preserve beta-cell function, further emphasizing the importance of early genetic testing [26].

Insulin and Continuous Glucose Monitor (CGM) Use in Infants

Most patients with heterozygous *INS* mutations will require lifelong insulin therapy, as in the case of many other forms of congenital diabetes. Continual improvements and advancements in types of insulin, insulin delivery devices including continuous subcutaneous insulin infusion systems (CSII; insulin pumps), and continuous glucose monitors will be valuable to these patients. One study analyzed insulin and CGM use in four infancy-onset diabetes cases; those using CSII were able to more accurately dose small quantities of insulin and did not experience any episodes of diabetic ketoacidosis (DKA) or severe hypoglycemia [86]. Analysis of a cohort of German patients helped to inform initial insulin dosing guidelines for neonates and infants [87•], and a comprehensive review on insulin therapy in infants has been published [88].

6q24: Transient Congenital Diabetes Related to Over-expression of Imprinted Genes

A variety of mechanisms can lead to over-expression of imprinted genes at chromosome 6q24, leading to severe intrauterine growth restriction and the most common cause of transient congenital diabetes [1, 2–4]. The hyperglycemia in these cases is often identified within the first few days of life and resolves spontaneously within the first year of life, but it returns later, usually around adolescence. However, two atypical cases of 6q24-related diabetes have recently been reported, including a case of permanent diabetes (still insulin-requiring at age 5.5 years) [5] and a case that did not have hyperglycemia during the infancy period [6]. Insulin is frequently used, although non-insulin therapies, particularly sulfonylureas, have been beneficial in some cases [7–9].

GATA6 and *GATA4*: Pancreatic Hypoplasia/Agenesis and Congenital Heart Defects

Heterozygous inactivating mutations in *GATA6* are the most common cause of pancreatic agenesis [73]. *GATA6* encodes for a transcription factor that plays a key role in the development of many tissues, including the pancreas, heart, and liver. Phenotypic characteristics include pancreatic hypoplasia or complete agenesis, infancy-onset diabetes, congenital heart defects, pancreatic exocrine insufficiency, and gallbladder or liver abnormalities. However, phenotypes may be variable based on the specific mutation, or even among family members with the same mutation [74]. One case study reported a mother with congenital heart defects (patent ductus arteriosus and atrial septal defect), but in whom diabetes was not diagnosed until after her third pregnancy at age 28, whereupon she was ultimately found to have agenesis of the dorsal pancreas [75]. Two of her children died shortly after birth, a third had DKA at 2 years of age and expired from secondary infection, while the fourth had Tetralogy of Fallot diagnosed at birth but did not develop diabetes until age 14 years and was found to have dorsal pancreatic agenesis. A large cohort of *GATA6* patients confirms the variability in age at diabetes diagnosis ranging from infancy (1 day old) to adult onset (46 years old), as well as some patients without diabetes [76]. Congenital heart defects were identified in 83% of patients, while a range of exocrine insufficiency (requiring enzyme replacement, subclinical deficiencies), hepatobiliary defects (gallbladder agenesis, biliary atresia), intestinal malformations (malrotation, hernias), hypothyroidism, and neurodevelopmental delays were also variably present. In a separate study, pancreatic histology from a donor patient with diabetes since 16 years of age and a missense mutation in *GATA6* revealed a severely atrophied pancreas, with some beta cells with severe amyloidosis, similar to the histopathology of patients with type 2 diabetes [89]. Similar to GATA6, GATA4 is a transcription factor that is required for normal pancreatic development. Mutations in *GATA4* can cause variable phenotypes which may include pancreatic hypoplasia or complete agenesis, diabetes (range from infancy-onset to childhood-onset), exocrine insufficiency, congenital heart defects, neurodevelopmental delay, and abnormal MRI findings [77]. We would recommend consideration of genetic testing in any patient with diabetes in conjunction with congenital heart defects or severe intestinal malformations, regardless of the age of onset of the diabetes.

Rarer Causes of Congenital Diabetes

RFX6: Diabetes, Intestinal Atresia, Gall Bladder Hypoplasia, and Diarrhea

RFX6 encodes for a transcription factor that is key to beta-cell differentiation, and the resulting recessively inherited syndrome consists of pancreatic (infancy-onset diabetes, pancreatic hypoplasia) and intestinal manifestations (intestinal atresia, gall bladder hypoplasia or agenesis and pancreatic enzyme replacement-unresponsive congenital diarrhea) [1, 49, 50]. Recent cases have been described with an expanded phenotype, including compound heterozygous cases with childhood-onset diabetes [51] and heterozygous cases with a MODY-like phenotype with reduced penetrance [52•].

IER3IP1: Diabetes with Microcephaly and Infantile Seizures

A syndrome of congenital diabetes, simplified gyral pattern microcephaly, and severe infantile-onset epileptic encephalopathy has been described in cases with homozygous, and now compound heterozygous mutations [53], in *IER3IP1*, a gene that may help to protect cells from stress-induced apoptosis [1].

NEUROG3: Intractable Diarrhea from Birth with Early-Onset Diabetes

Recessive mutations in *NEUROG3*, a transcription factor involved in pancreatic and enteroendocrine development and function, have been reported to cause congenital diabetes with variable ages of onset and chronic intractable malabsorptive diarrhea [1, 46]. Recently, additional features have been described, including hypogonadotropic hypogonadism and short stature, emphasizing the need for screening and treatment when indicated [47]. Previously, *NEUROG3* was thought to be critically essential for differentiation of endocrine cells. However, cases with evidence of endogenous insulin production (detectable c-peptide levels) have been reported, suggesting that at least some limited differentiation may still be possible when this gene is disrupted [48].

NEUROD1: Diabetes with Cerebellar Hypoplasia without Pancreatic Exocrine Dysfunction

NEUROD1 encodes for a transcription factor that is highly expressed in both developing and mature beta cells, mutations in which have been reported to cause MODY (heterozygous) [44] or infancy-onset diabetes (homozygous) [1, 45]. Infancy-onset cases may exhibit cerebellar hypoplasia, developmental delay, sensorineural deafness, and visual impairment without pancreatic exocrine insufficiency.

PTF1A: Diabetes with Cerebellar and Pancreatic Hypoplasia with Exocrine Dysfunction

PTF1A encodes a transcription factor that is essential for specification of pancreatic endocrine, exocrine, and ductal cells [1]. Clinical characteristics of patients with recessive mutations in *PTF1A* may include flexion contractures of arms and legs, paucity of subcutaneous fat and optic nerve hypoplasia, complete agenesis of the cerebellum, and complete absence of the pancreas [42]. However, cases with reduced severity have been described, including recently reported cases of isolated congenital diabetes and exocrine insufficiency without neurodevelopmental delay [43]. Whole-genome sequencing identified mutations in a distal enhancer region regulating *PTF1A*, which render the enhancer dysfunctional and cause isolated pancreatic agenesis [90, 91].

GLIS3: Diabetes and Congenital Hypothyroidism

Homozygous mutations in *GLIS3* have been reported to cause infancy-onset diabetes, congenital primary hypothyroidism, and mild facial dysmorphism [1, 56]. These facial features were analyzed in detail for seven patients and include eye (elongated palpebral fissures), ear (low-set), nose (upturned; depressed nasal bridge), and mouth (long philtrum; thin dark border of the upper lip) characteristics [57]. Liver fibrosis and polycystic kidneys have been reported rarely [58]. *GLIS3* plays an important role in insulin gene transcription, beta cell survival, and insulin secretion, which may help to explain how variants can cause

monogenic disease (congenital diabetes) as well as contribute to polygenic conditions (type 1 and type 2 diabetes) [59].

PDX1: Congenital Diabetes with Pancreatic Hypoplasia and Exocrine Dysfunction

Homozygous mutations in *PDX1* leading to pancreatic agenesis were the first discovered genetic cause of permanent congenital diabetes, with additional cases since described due to compound heterozygous mutations with some degree of phenotypic variability [1, 38]. Pancreatic hypoplasia or agenesis is a distinguishing feature, along with significant, subclinical, or undetectable exocrine insufficiency [39]. Heterozygous mutations in the same gene can cause MODY [40], although it is important to note that about 5% of individuals sequenced in the UK were found to have variants in *PDX1* that did not cause diabetes, thus emphasizing the rare nature of true PDX1-MODY [41].

HNF1B: Infancy-Onset Diabetes with Renal Anomalies

Only a few cases of infancy-onset diabetes have been reported to be caused by heterozygous mutations in *HNF1B*, though 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) [1]. Clinical characteristics may include intermittent insulin requirements, dysplastic kidneys, kidney cysts, pancreatic hypoplasia, and/or exocrine insufficiency [54, 55]. There is more commonly an incomplete penetrance of diabetes within these families, while renal and/or genitourinary abnormalities tend to be consistent features.

PAX6: Infancy-Onset Diabetes with Brain Malformations, Microcephaly, and Microphthalmia

Both heterozygous and biallelic mutations in *PAX6*, a paired domain-containing transcription factor involved in islet cell differentiation and function, have been described [1]. Heterozygous carriers may exhibit ocular anomalies, impaired glucose tolerance, and/or elevated proinsulin/insulin levels in response to a glucose challenge [60]. Homozygous cases present with more severe phenotypes, including infancy-onset diabetes, brain malformations, microcephaly, anopthalmia, and/or panhypopituitarism, with some cases not surviving past the first year of life [1, 61].

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

Diabetes has been reported as the earliest and most consistent feature of Wolfram syndrome (caused by recessive mutations in *WFS1*), with subsequent development of optic atrophy, then later onset of diabetes insipidus and/or deafness (DIDMOAD syndrome), although phenotypes can be variable [1, 62, 63]. Age of onset can vary from the first year of life to early childhood. Functionally, *WFS1* is thought to regulate ER stress, and decreased function leads to cell death in pancreatic islets as well as other tissues. In the heterozygous state, cases with isolated features such as diabetes or deafness have been reported. However, a recent paper demonstrated a distinct type of severe, heterozygous mutations which caused infancy-onset diabetes (median diagnosis age 35 weeks, range 13–50 weeks), deafness, cataracts, and hypotonia by inducing a significant level of ER stress [64].

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

Mutations in *SLC19A2*, which encodes a plasma membrane thiamine transporter (THTR1), have been reported as the cause of TRMA (Rogers syndrome), with diabetes diagnosed at variable ages, including infancy onset [1, 65]. Clinical characteristics include diabetes, megaloblastic anemia, and sensorineural deafness. Both the anemia and the diabetes may be responsive to thiamine treatment. A recent case study of a patient with a novel *SLC19A2* mutation reported an increase in fasting C-peptide levels after 3 months of thiamine treatment and a subsequent decrease in insulin requirements [92]. By 23 months old, after 11 months of thiamine treatment, the patient's C-peptide had increased by 0.24 ng/mL, and the patient no longer required insulin treatment.

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

Fanconi-Bickel syndrome (FBS) is caused by homozygous or compound heterozygous mutations in *SLC2A2*, which encodes the facilitative glucose transporter, GLUT2 [1, 66]. Clinical characteristics of FBS may include hepatomegaly related to hepatic and renal glycogen accumulation, renal proximal tubular dysfunction characterized by glucosuria and phosphate wasting often leading to hypophosphatemic rickets, delay of puberty and short stature, hypergalactosemia (which may be identified by newborn screening), and mild fasting hypoglycemia but postprandial hyperglycemia and diabetes or impaired glucose tolerance at many ages of onset, including during infancy [93, 94]. The heterogeneity of this syndrome was further elucidated in a recent report of three siblings, one of whom had transient infancy-onset diabetes (onset around 2 weeks old, remission at 3 months old), as well as hepatomegaly, phosphaturia, hypercalciuria, aminoaciduria, and proximal renal tubular acidosis [95]. Diabetes was not present in the other two siblings, although one did experience fasting hypoglycemia, and unfortunately, they both died (age 4 months and age 6 years).

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

EIF2AK3 encodes fora translation-regulating kinase that plays an important role in the trafficking of proinsulin in beta cells [1, 27]. Recessive mutations cause Wolcott-Rallison syndrome (WRS), which may consist of epiphyseal dysplasia (not always obvious, radiographs may be helpful), liver or renal dysfunction, epilepsy, developmental delay, and infancy-onset diabetes [28, 29].Autopsy results from two patients with WRS revealed changes attributed to endoplasmic reticulum stress (hepatocytes, exocrine cells), steatosis (renal tubular cells, hepatocytes, myocardial fibers), abnormal mitochondria (renal and myocardial fibers), and a reduction in beta cells [30].

GCK: Isolated Congenital Diabetes Due to Recessive Mutations

Recessive mutations in the gene encoding the glycolytic enzyme glucokinase (*GCK*) cause infancy-onset diabetes without other syndromic features [1, 33]. Although rare in the USA and European registries, the frequency of these cases may be higher in countries with high rates of consanguinity, as reported in a recent paper from Oman [34]. Most cases will require

lifelong insulin therapy, although partial responsiveness to repaglinide and the sulfonylurea glibenclamide have been reported [1]. Phenotypic heterogeneity has been described across recessive mutations, including atypical features such as childhood-onset diabetes, with protein instability playing the largest role in predicted severity [35]. In the heterozygous state, *GCK* mutations cause stable, mildly elevated fasting blood glucose levels without diabetes-related complications (GCK-MODY, [36, 37]).

MNX1 and NKX2–2: Diabetes and Central Nervous System Malformations

A study of consanguineous families revealed homozygous mutations in both *NKX2–2* and *MNX1* as causes of congenital diabetes [71]. *NKX2–2* encodes for a transcription factor that is critically important for both pancreatic and central nervous system development. Clinically, patients with these mutations presented with intrauterine growth restriction (IUGR) (birthweight standard deviation range – 2.8 to – 4.52), diabetes (diagnosis age 2–7 days), developmental delay (moderate to severe), hypotonia, blindness, and hearing impairment but had normal exocrine function. *MNX1* encodes for a transcription factor that plays an important role in pancreatic development and function [72]. As compared to patients with *NKX2–2* mutations, some similarities in clinical features exist for patients with homozygous *MNX1* mutations, including IUGR (birthweight standard deviation range – 2.54 to – 3.09) and infancy-onset diabetes (diagnosis age 1–30 weeks). However, one *MNX1* patient experienced developmental delay (severe), short stature (< 3rd percentile), neurological complications, hypoplastic lungs, sacral agenesis, high imperforate anus, and other severe features that were not seen in the other *MNX1* patient, which was attributed to mutation severity.

Monogenic Causes of Autoimmune Dysfunction Including Diabetes

Several monogenic forms of autoimmune dysfunction have been associated with diabetes.

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

Mutations in the X-linked gene *FOXP3* are a rare cause of infancy-onset monogenic autoimmune diabetes, along with numerous other features including enteropathy causing severe diarrhea and malnutrition, severe eczema, and autoimmune thyroid disease [1]. Patients with the classically described syndrome have a severe clinical course, resulting in death within the first few years of life without stem cell transplant; however, ongoing reports demonstrate the phenotypic spectrum of cases who may only have diabetes in isolation [31, 32].

Additional Causes of Autoimmune Dysfunction

Mutations in *AIRE*, an autoimmune regulator, had been previously associated with a syndrome called APECED, autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy, which can include autoimmune diabetes, although the diagnosis age in these cases is typically outside of infancy [96, 97]. Biallelic mutations in *LRBA* cause severe autoimmune disease, including infancy-onset diabetes, as described in a cohort of nine patients (diabetes diagnosis range 6 weeks–15 months) with additional features including

hematological, gastrointestinal, and endocrine disorders, as well as recurrent infections [67]. *IL2RA* encodes for the interleukin 2 receptor alpha chain, which constitutes a portion of the interleukin-2 receptor [68]. Interleukin-2 is an important cytokine in the immune system, and mutations in *IL2RA* can cause autoimmune disorders including infancy-onset diabetes. One case presented with diabetes, severe diarrhea, and respiratory failure at age 6 weeks. He was diagnosed with autoimmune enteropathy and later a series of conditions including developed eczema, systemic lymphadenopathy, hepatosplenomegaly, enlarged tonsils, sleep apnea, hypothyroidism, and hemolytic anemia [68]. STAT1 and STAT3 are two members of the STAT protein family, which act as transcriptional activators, and mutations in these genes have also been reported to cause infancy-onset autoimmune diabetes. Five patients with polyautoimmunity were found to have uniallelic mutations in *STAT1*; three were diagnosed with autoimmune diabetes (diagnosis ages 11 months–5 years), and another had episodes of hyperglycemia while on steroids [69]. Multiple other autoimmune conditions were present in each case. A cohort of five patients with *STAT3* mutations has been described, three of whom had diabetes (diagnosis ages birth–43 weeks) [70•], in addition to several other autoimmune conditions. A type 1 diabetes genetic risk score may help in differentiating individuals with polygenic autoimmune type1 diabetes from those who may have a monogenic autoimmunity syndrome [98].

General Considerations Regarding Diagnosis and Etiology of Congenital Diabetes

Importance of Early Diagnosis and Treatment

Diabetes onset in infancy can be particularly severe, with a primarily US-based cohort reporting that 66% of participants were in diabetic ketoacidosis (DKA) at the time of diagnosis [99•]. In the same cohort, the odds of DKA increased with diagnosis age—the odds ratio per 1 month increase was 1.23 (95% CI 1.04, 1.45). DKA is associated with increased morbidity and mortality, is costly to the healthcare system, and is stressful for families, further emphasizing the need for promoting efforts at earlier recognition of symptoms of diabetes before DKA develops. Once diabetes is diagnosed during the first year of life, genetic testing should be pursued without delay in order to guide appropriate therapy, evaluation of possible associated features, and family testing. Two large studies have shown that there can be significant delay between the time of diagnosis of diabetes and the genetic diagnosis [100, 80••]. In the USA, this is often related to the coverage of the cost of clinical testing, whereas in the cohort from the UK, the delay has improved considerably over the years, from ~ 4 years in 2005 to ~ 3 months after 2012.

Cost-Effectiveness of Genetic Testing in Monogenic Diabetes

A significant cost-savings results from a policy of genetic testing of infants diagnosed with diabetes under 6 months of age compared to a policy of not testing, largely because of the dramatic improvement in glycemic control and improved long-term outcomes for patients with KATP-related congenital diabetes who can be treated with oral sulfonylureas [101]. As more cases with congenital diabetes are discovered with diagnoses between 6 and 12 months of age (University of Chicago Monogenic Diabetes Registry, data unpublished), additional

analyses on cost-effectiveness of testing in this age group will be important, particularly for those in whom treatment may not change (such as patients with *INS* mutations). We recommend performing genetic testing on any patient diagnosed with diabetes under 12 months of age. Performing genetic testing for GCK-, HNF1A-, and HNF4A-MODY in selected populations was shown to be cost-effective, with increased effectiveness as MODY prevalence increased in the selected population or as testing costs decreased [102].

The Future of Genetic Testing in Congenital Diabetes

Given the long and growing list of genes known to cause congenital diabetes, it has become increasingly difficult to sequence all possible genes using traditional methods that are time-consuming, labor-intensive, and expensive. Furthermore, most gene causes have significant clinical heterogeneity; thus, phenotype-based selection of genes to be tested is unreliable and could result in a delayed or missed diagnosis. Methods such as next-generation sequencing (NGS), which allow hundreds of genes to be analyzed in one run, have become cheaper and more readily available. These “panel” tests can be fully customized with known genes, research genes of interest, and important regulatory regions [103]. Prices vary between commercial and research labs, but this approach may be more efficient and/or cost-effective than single gene sequencing. A large cohort study from the UK tested 1020 patients using a combination of [1] rapid Sanger sequencing for the most common causes (*KCNJ11*, *ABCC8*, *INS*, and methylation analysis for 6q24 abnormalities) followed by [2] a customized NGS panel which covered all known congenital diabetes genes [93]. Using this comprehensive method, they were able to find a monogenic cause in 82% of patients diagnosed under 6 months of age. The success in identifying a monogenic cause was similar for consanguineous and non-consanguineous cases. Even more comprehensive methods, such as whole exome and whole genome sequencing, are also becoming more affordable. While these methods are attractive because they increase opportunities for gene discovery, they also generate significantly more data, which can make interpreting variants more difficult. Improvements in bioinformatics and increased collaboration between clinical researchers and those performing functional work will help to improve the reliability of interpretation.

Conclusion

Mutations in nearly 30 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 80–85% of patients with permanent congenital diabetes diagnosed under 6 months, suggesting that continuing research will identify new genes and/or regulatory regions. Due to the potential implications for treatment and for family members, we recommend genetic testing for any patient diagnosed with diabetes under a year of age. Decreasing costs and improving technologies will allow for better access to early, comprehensive genetic testing. Finally, expansion in both molecular and clinical research will help to facilitate improvements in diabetes treatment, as well as prognosis and care of associated features.

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Abbreviations

MODY	Maturity onset diabetes of the young
DPP-IV	Dipepdidyl-peptidase-IV
ER	Endoplasmic reticulum
KATP channel	ATP-sensitive potassium channel
MRI	Magnetic resonance imaging
CSII	Continuous subcutaneous insulin infusion
CGM	Continuous glucose monitor
AGA	Appropriate for gestational age

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Table 1

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

Gene	Protein/fimction	Phenotypes/syndromes	Inheritance	Age of diabetes onset	Pancreas appearance/exocrine function	Other features	Ref
PLAGL1 HYMAI (6q24)	Over-expression of paternally expressed genes *PLAGL1* (zinc finger protein or ZAC tumor suppressor) and *HYMAI* (non-protein coding) within the imprinted region of chromosome 6q24/unknown function	TNDM	UPD6 (40%; de novo, non-recurrent), paternal duplication (40%, may be inherited) or maternal methylation defect (20%; autosomal recessive, e.g. *ZFP57*)	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 *ZFP57* mutations (see below)	[2–9]
ZFP57	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)	[2–9]
KCNJ11	Inward rectifier K(+) channel (Kir6.2) subunit of ATP- sensitive potassium channel	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	[10–21•]
ABCC8	Sulfonylurea receptor 1 (SURI) subunit of ATP-sensitive potassium channel	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	[10–21•]
INS	Insulin/hormone	PNDM (more often), TNDM (rarely), MODY (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	[22–26]
EIF2AK3	Eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2 AK3)/kniase 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 (90–100%); acute liver failure (60–75%); developmental delay (60–80%); hypothyroidism (−25%); exocrine pancreatic dysfunction (−25%)	[27–30]
FOXP3	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	[31–32]

Gene	Protein/fimction	Phenotypes/syndromes	Inheritance	Age of diabetes onset	Pancreas appearance/exocrine function	Other features	Ref
						(30%); often die before 1 year	
GCK	Glucokinase/glycolytic enzyme	PNDM; GCK-MODY	Autosomal recessive (PNDM); or autosomal dominant (GCK-MODY)	PNDM days of life MODY2 present from birth but not usually detected until later	Normal/normal	PNDM: Very SGA, 12/14 homozygous, 1/14 compound heterozygous, 1/14 heterozygous (unclear mechanism), parents have impaired fasting glucose with GCK-MODY (MODY2)	[33–37]
PDX1	Pancreas/duodenum homeobox protein 1 (PDX1 orlPFl)/ transcription factor	PNDM with pancreatic agenesis/ hypoplasia PDX1-MODY (heterozygous)	Autosomal recessive; Autosomal dominant (PDX1-MODY)	3/5 cases within days; 2/5 cases 12–15 days	Absent (1/5), small (3/5) or normal (l/5)/ absent (3/5) or reduced (2/5)	SGA; diarrhea; malnutrition; parents have PDX1 MODY (MODY4)	[38–41]
PTF1A	Pancreas transcription factor 1, subunit alpha (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	[42–43]
NEUROD1	(NeuroDl or BETA2)/bHLH transcription factor	PNDM with cerebellar (but not pancreatic) hypoplasia MODY-like (heterozygous)	Autosomal recessive; Autosomal dominant (MODY-like)	2 cases by 2 months	Normal/normal	SGA; severe cerebellar hypoplasia; moderate to severe developmental delay; sensorineural deafness; visual impairment MODY-like	[44–45]
NEUROG3	(NeuroG3 or NGN3)/bHLH transcription factor	PNDM with severe congenital diarrhea	Autosomal recessive	2/5 cases within days; 2/5 cases by 9 yrs	Small/4/5 normal	Very SGA; severe intractable congenital diarrhea unresponsive to pancreatic enzyme replacement with absent intestinal enteroendocrine cells; hypogonadotropic hypogonadism; short stature	[46–48]
RFX6	DNA-binding protein (RFX6)/ winged-helix transcription factor	PNDM with intestinal atresia, gall bladder hypoplasia MODY- like (heterozygous)	Autosomal recessive; Autosomal dominant (MODY-like)	5 cases within days Compound heterozygote: childhood-onset RFX- MODY: 27 cases, median 32 years (IQR 24–46 years)	Small/nomial	Very SGA; intestinal atresias; gall bladder hypoplasia/aplasia; diarrhea MODY-like	[49–52•]
IER3IP1	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	[53]
HNF1B	Hepatocyte nuclear factor 1 - beta (HNF-1 ß)/ transcription factor	TNDM/PNDM; (RCAD; MODY5)	Spontaneous or autosomal dominant	2 cases 15–17 days	Hypoplastic/ reduced	Very SGA; renal abnormalities; relapsing/remitting DM	[54–55]

Gene	Protein/fimction	Phenotypes/syndromes	Inheritance	Age of diabetes onset	Pancreas appearance/exocrine function	Other features	Ref
						(RCAD: renal cysts, urogenital abnormalities)	
GLIS3	Glioma-associated oncogene- similar family zinc finger 3 (GLIS3)/Kriippel-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); facial dysmorphism	[56–59]
PAX6	Paired box 6/paired box and horneo domain box containing transcription factor	PNDM with severe microcephaly and eye defects	Autosomal recessive	2 brothers within days (other case: DM not reported)	Normal/not reported	Brain malformations; microcephaly; micropthalmia (eye defects in parents); panhypopituitarism	[60–61]
WFS1	Wolframin/membrane glycoprotein	Wolfram syndrome; DIDMOAD	Autosomal recessive; Autosomal dominant	Recessive: Median 6 yrs.(3 wks–14 yrs) Dominant: range 13–50 weeks	Normal/normal	Optic atrophy (earliest feature); diabetes insipidus; deafness; cataracts; hypotonia	[62–64]
SLC19A2	Thiamine transporter 1/transports thiamine across the plasma membrane	Thiamine-responsive megaloblastic anemia (TRMA) syndrome	Autosomal recessive	12 cases 2–13 months; Others: DM later	Normal/normal	Thiamine-responsive megaloblastic anemia; sensorineural deafness; occasional CHD (conduction defects); short stature	[65]
SLC2A2	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,	[66]
LRBA	Lipopolysaccharide-responsive nd beige-like anchor protein/ vesicle trafficking	PNDM,polyautoimmunity	Autosomal recessive	In 10 cases, 6 weeks–15 months	Normal/normal	Autoimmune conditions	[67]
IL2RA	Interleukin-2 receptor subunit alpha/ membrane protein and receptor for interleukin-2	PNDM,polyautoimmunity	Autosomal recessive	In 1 case, 6 weeks	Normal/normal	Autoimmune conditions	[68]
STAT1	Signal transducer and activator of transcription 1-alpha/beta/ transcription activator	PNDM,polyautoimmunity	Autosomal dominant	In 5 cases, 11 months-5 years (one did not have diabetes, one had hyperglycemia in response to steroids)	Normal/normal	Autoimmune conditions	[69]
STAT3	Signal transducer and activator of transcription 3/transcription activator	PNDM,	Autosomal dominant	In 5 cases, 0–43 weeks (one did	NormaFnormal	Autoimmune conditions; short stature	[70•]

Gene	Protein/fimction	Phenotypes/syndromes	Inheritance	Age of diabetes onset	Pancreas appearance/exocrine function	Other features	Ref
				not have diabetes)			
MNX1	Motor neuron and pancreas homeobox protein 1/nuclear protein	polyautoimmunity PNDM	Autosomal recessive	In 2 cases, 1–30 weeks	NormaFnormal	Brain malformations; SGA/growth concerns; intestinal malformations; developmental delay; lung hypoplasia; short stature	[71–72]
NKX2–2	Homeobox protein Nkx-2.2/ morphogenesis of the central nervous system	PNDM	Autosomal recessive	In 3 cases, 2–7 days	NormaFnormal	Brain malformations; hearing impairment; SGA/growth concerns; eye malformations/ blindness; developmental delay; short stature	[71]
GATA6	Transcription Factor GATA-6/zinc finger transcription factor	PNDM, occasionally later-onset	Autosomal dominant	In 24 cases, median 2 days (IQR 1–7 days); Others: DM later	Agenesis or hypoplasia/reduced	SGA/growth concerns; CHD; intestinal malformations; developmental delay; thyroid dysfunction; hepatobiliary defects	[73–76]
GATA4	Transcription Factor GATA-4/zinc finger transcription factor	PNDM	Autosomal dominant	In 5 cases, range 1 day-13 years	Agenesis or hypoplasia/normal or reduced	SGA/growth concerns; CHD; intestinal malformations	[77]

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TNDM transient neonatal diabetes, *PNDM* permanent neonatal diabetes, *DEND* developmental delay, epilepsy, neonatal diabetes, WS5 Wolcott-Rallison syndrome, *IPEX* immunodysregulation polyendocrinopathy, enteropathy, x-linked, *MODY* maturity-onset diabetes of the young, *DIDMOAD* diabetes insipidus, diabetes mellitus, optic atrophy and deafness, *TRMA* thiamine-responsive megaloblastic anemia syndrome, *FBS* Fanconi-Bickel syndrome, *NDH* neonatal diabetes with congenital hypothyroidism, *RCAD* renal cysts and diabetes, *bHLH basic* helix-loop-helix, *SGA* small for gestational age, *MODY* maturity-onset diabetes of the young, *CEID* congenital heart defect, *EIIL* hypomethylation of multiple imprinted loci

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Table 2

Clinical features associated with multiple monogenic causes of congenital diabetes

Clinical feature	Genes to consider testing
Neurodevelopmental disability	*KCNJ11, ABCC8, EIF2AK3, GLIS3, NEUROD1, PTF1A, PAX6, IER3IP1, MNX1, NKX2–2,* 6q24 abnormalities, *GATA6*
Diarrhea and/or exocrine pancreatic insufficiency	*GATA6, GATA4, NEUROG3, FOXP3, PDX1, PTF1A, RFX6, GLIS3, HNF1B, EIF2AK3, LRBA, IL2RA, STAT1, STAT3*
Thyroid dysfunction	*GLIS3, FOXP3, EIF2AK3, IL2RA, GATA6*
Transient or relapsing/remitting diabetes	6q24 abnormalities, *ZFP57, KCNJ11, ABCC8, INS, HNF1B, SLC2A2, SLC19A2*
Family history of diabetes	Both parents or in their families: *GCK, PDX1, NEUROD1, PTF1A, RFX6, WFS1, INS* (recessive mutations upstream of coding region or deletions)
	One parent (infancy or adult onset): *ABCC8, KCNJ11, INS, HNF1B, GCK,* 6q24 duplications (paternally inherited), *GATA6*
Kidney structural or functional defects	*HNF1B* (structural anomalies and/or cysts), *GLIS3* (cysts), *EIF2AK3* (acute renal failure), *SLC2A2* (tubular dysfunction with glucosuria and phosphaturia), *WFS1* (diabetes insipidus)
Liver dysfunction	*EIF2AK3* (episodic liver failure), *SLC2A2* (hepatomegaly without liver failure), *RFX6* (gall bladder hypoplasia with intestinal atresia and malformations), *GLIS3* (liver fibrosis in some cases), *GATA6* (hepatobiliary defects such as gallbladder agenesis or biliary atresia)
Skeletal abnormalities	*EIF2AK3* (epiphyseal dysplasia will be apparent radiographically if not clinically), *GLIS3* (osteopenia with elevated alkaline phosphatase), *PTF1A* (flexion contractures of arms/legs), *SLC2A2* (hypophosphatemic rickets)
Visual impairment	*PAX6* (aniridia, microphthalmia, also in parents), *NEUROD1, WFS1* (optic atrophy outside infancy period), *PTF1A* (optic nerve hypoplasia), *GLIS3* (congenital glaucoma), *NKX2–2* (cortical blindness)
Deafness	*WS1, SLC19A2, NEUROD1, GLIS3, NKX2–2*
Megaloblastic anemia or other hematological disorder	*SLC19A2, FOXP3, LRBA*
Autoimmune conditions	*FOXP3, LRBA, IL2RA, STAT1, STAT3, AIRE*
Short stature	*FOXP3, STAT1, STAT3, MNX1, NKX2–2, SLC19A2*

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