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Monogenic diabetes: a gateway to precision medicine in diabetes

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Monogenic diabetes refers to diabetes mellitus (DM) caused by a mutation in a single gene and accounts for approximately 1%–5% of diabetes. Correct diagnosis is clinically critical for certain types of monogenic diabetes, since the appropriate treatment is determined by the etiology of the disease (e.g., oral sulfonylurea treatment of *HNF1A*/*HNF4A*-diabetes vs. insulin injections in type 1 diabetes). However, achieving a correct diagnosis requires genetic testing, and the overlapping of the clinical features of monogenic diabetes with those of type 1 and type 2 diabetes has frequently led to misdiagnosis. Improvements in sequencing technology are increasing opportunities to diagnose monogenic diabetes, but challenges remain. In this Review, we describe the types of monogenic diabetes, including common and uncommon types of maturity-onset diabetes of the young, multiple causes of neonatal DM, and syndromic diabetes such as Wolfram syndrome and lipodystrophy. We also review methods of prioritizing patients undergoing genetic testing, and highlight existing challenges facing sequence data interpretation that can be addressed by forming collaborations of expertise and by pooling cases.

Introduction

Monogenic diabetes is caused by a single defect in one of over 40 genes (1, 2). Since maturity-onset diabetes of the young (MODY) was named by Fajans for the type 2 diabetes–like presentation in young people with an autosomal dominant pattern of inheritance (3, 4), our understanding of phenotypic and genetic heterogeneity in monogenic diabetes has increased. The major monogenic diabetes categories are MODY, neonatal diabetes mellitus (NDM), and syndromic diabetes (5). Misdiagnosis is frequent because of overlapping of phenotypes with type 1 diabetes (T1D), such as young onset and leanness, and with type 2 diabetes (T2D), such as preserved β cell function and family history. Tailored treatment of some monogenic diabetes depends on the disease's underlying etiology — e.g., oral sulfonylurea treatment of *HNF1A*/*HNF4A*-MODY — and requires genetic testing to diagnose. Here we will describe monogenic diabetes types, etiologies, diagnosis, management, and strategies to improve diagnosis.

Monogenic versus polygenic diabetes

Monogenic and polygenic diabetes are traditionally considered distinct, with monogenic diabetes resulting from one highly penetrant variant in one gene in a given individual and polygenic diabetes resulting from the contribution of several variants with smaller effects in the context of environmental/lifestyle factors. In T1D, autoimmune dysfunction is the prominent mechanism, with variation in the major histocompatibility locus and other genomic factors combining with apparent environmental triggers to result in β cell loss and diabetes. In monogenic diabetes, highly penetrant variants, mostly causing extremely impaired β cell development and insulin secretion, cause diabetes regardless of other risk factors. T2D, sometimes considered a diagnosis of exclusion, is a heterogeneous group of disorders involving smaller genetic effects on multiple mechanisms, including insulin secretion and insulin sensitivity, combining with environmental and lifestyle factors, mostly impacting insulin sensitivity. While this distinction is important both scientifically and clinically, emerging studies of the genetic architecture of diabetes reveal more of a spectrum with respect to the penetrance of genetic variants and their relative role in diabetes. For example, the *HNF4A* variant p.R114W, found in 0.02% of non-Finnish Europeans, has been shown to be overrepresented in patients with MODY (OR = 30.4 vs. public variant databases) but to have a distinct clinical phenotype (including lack of sulfonylurea response) and much lower penetrance than other *HNF4A* MODY mutations (54% vs. 71% by age 30; ref. 6). In Mexican Americans, *HNF1A* variant p.E508K (NM_000545.8, rs483353044) was associated with T2D with a much greater effect size (OR = 4.2) than most polygenic T2D variants, with diabetic carriers and noncarriers having similar onset age and BMI (7). T2D polygenic risk scores have also shown evidence of modifying age at diagnosis of monogenic diabetes (8). Finally, while lack of features of either autoimmunity or obesity/metabolic syndrome raises the likelihood of monogenic diabetes, these features can coexist with monogenic diabetes — particularly obesity, given its high prevalence especially in youth. In the Treatment Options for Diabetes in Adolescents and Youth (TODAY) clinical trial, in which overweight or obesity was required for enrollment of newly diagnosed youth with T2D, at least 4.5% were identified as having MODY. Those with *HNF4A*-MODY had poor response to metformin, representing a previously missed opportunity for optimal

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Table 1. Genetic causes of maturity-onset diabetes of the young

Gene/MODY number (OMIM number)	Age of onset	Treatment	Distinguishing features	Pathophysiology	References
HNF4A/MODY1 (125850)	Preadolescence to young adulthood	Low-dose sulfonylureas	Neonatal macrosomia and hyperinsulinemic hypoglycemia	Transcription factor defect disrupting β cell development and function	16
GCK/MODY2 (125851)	Birth	None (except during pregnancy when insulin may be required if fetus does not inherit variant)	Lifelong mild fasting hyperglycemia, low postprandial glucose increment; usually neither responds to nor requires treatment. No increased risk of micro- and macrovascular complications	Impaired β cell glucose sensing	25
HNF1A/MODY3 (600496)	Preadolescence to young adulthood	Low-dose sulfonylureas	Low renal threshold for glucose	Transcription factor defect disrupting β cell development and function	16
PDX1/MODY4 (606392)	Young adulthood	OHA or insulin	Pancreatic agenesis in homozygotes/compound heterozygotes (rare)	Transcription factor defect disrupting β cell development and function	16, 141–144
HNF1B/MODY5 (137920)	Preadolescence to young adulthood	Insulin	Renal structural abnormalities, genital tract malformations, pancreatic hypoplasia, hypomagnesemia, abnormal liver function, intellectual disabilities	Transcription factor defect disrupting β cell and renal cell development and function	56
NEUROD1/MODY6 (606394)	Young adulthood	Insulin	Reduced penetrance for diabetes	Transcription factor defect disrupting β cell development and function	145
CEL/MODY8 (609812)	Young adulthood	Insulin	Pancreatic exocrine dysfunction in childhood and diabetes in later adulthood with multiple pancreatic cysts	Unclear	146–148
INS/MODY10 (176730)	Childhood to young adulthood	Diet or insulin	Specific mutations cause insulin dependence due to ER stress–mediated β cell apoptosis	Proinsulin misfolding and ER stress or impaired insulin activity	76, 149–154
ABCC8/MODY12 (600509)	Preadolescence to young adulthood	Sulfonylureas	Neurological abnormalities in some cases	Gain of function β cell ATP-sensitive potassium channel defect	76, 153, 154
KCNJ11/MODY13 (616329)	Childhood	Sulfonylureas	Neurological abnormalities in some cases	Gain of function β cell ATP-sensitive potassium channel defect	76, 146–148, 153, 154
RFX6	Varies	Diet, insulin, or OHA	Reduced penetrance for diabetes	Transcription factor defect disrupting β cell function	11

BLK, *PAX4*, and *KLF11*, although classified as MODY genes (#11, #9, and #7, respectively) in OMIM, are not listed as MODY-causing because of recently disputed or refuted gene-disease relationships (see "Rare MODY-classified monogenic diabetes types" in the main text). *APPL1* was proposed as MODY14 based on two families reported in 2015 (42), but evidence is otherwise limited. *RFX6* does not have a MODY number in OMIM, but is included here as multiple loss-of-function variants were recently implicated in a phenotype very similar to that of other MODY genes but with lower penetrance (11). OHA, oral hypoglycemia agents.

treatment (9). In summary, monogenic and polygenic forms of diabetes exist along more of a continuum than previously appreciated. Therefore, knowledge about monogenic diabetes not only provides opportunities for etiology-based treatment of the minority of individuals with highly penetrant variants, but also informs broader understanding of diabetes etiology.

Types of monogenic diabetes

Maturity-onset diabetes of the young

MODY comprises most monogenic diabetes cases, with classical characteristics of young diagnosis age, family history of diabetes in an autosomal dominant pattern of transmission, and insulin independence, with some types having additional features (Table 1). While 14 genes have now been designated as MODY genes in OMIM and/or the literature, three of these (*BLK*, *PAX4*, and *KLF11*) have been proposed for elimination based on a recent study (10) (see Table 1 for the remaining 11 along with *RFX6*, recently proposed as an additional MODY gene; ref. 11). Variants in *GCK*, *HNF1A*, and *HNF4A* are responsible for most MODY cases, followed by *HNF1B* (12). Given the known genetic etiology of most MODY cases and the increased frequency of pediatric T2D due to increased childhood overweight and obesity prevalence, it has been suggested that this term be abandoned in favor of terms describing the etiology of the type of diabetes, such as transcription factor diabetes for MODY caused by mutations in the transcription factor genes *HNF1A*, *HNF4A*, *HNF1B*, and others (13). Moreover, it can be argued that any diabetes designation is unsuitable for the usually benign condition of heterozygous GCK deficiency, which is characterized by only mildly elevated glucose levels often not reaching the diabetic range and, more to the point, generally does not lead to diabetic micro- and macrovascular complications (14).

Common types of MODY-classified monogenic diabetes

HNF1A-MODY and *HNF4A*-MODY are caused by variants in genes encoding HNF1 homeobox A and hepatic nuclear factor 4α, respectively. These transcription factors play essential roles in transcription of genes related to β cell development and insulin secretion. *HNF1A* variants decrease expression of HNF1A target genes (15). Among patients diagnosed with diabetes, *HNF1A*-MODY is the most common MODY. To date, over 400 *HNF1A* variants and 100 *HNF4A* variants have been discovered from MODY families (16).

HNF1A/*HNF4A*-MODY is usually diagnosed in adolescence or early adulthood. Compared with T2D, *HNF1A*-MODY and *HNF4A*-MODY occur at younger ages with lower BMI, lower hemoglobin A_{1c} and triglycerides, and similar risk for microvascular complications. Approximately 50% of patients with *HNF4A*-MODY are macrosomic, which is attributed paradoxically to transient neonatal hyperinsulinemic hypoglycemia at birth (17). Hyperinsulinemic hypoglycemia was also recently observed in some patients with *HNF1A*-MODY (18).

Individuals with *HNF1A*- and *HNF4A*-diabetes have increased sensitivity to sulfonylureas, an insulin-stimulating class of drug (19, 20), such that low doses are effective, and more typical T2D doses cause hypoglycemia. Sulfonylureas bind to the subunit of the K_{ATP} channel to depolarize the β cell and release insulin. In a randomized clinical trial, low doses of sulfonylureas (e.g., 20–40 mg gliclazide daily) produced better glucose control than metformin in *HNF1A*- and *HNF4A*-MODY (21). In an observational study, most patients with presumed T1D who were subsequently found to have *HNF1A*-diabetes gained glycemic control when treatment was changed from insulin to sulfonylureas (19). Glucagon-like peptide-1 receptor agonist monotherapy (22) or sulfonylurea in combination with dipeptidyl peptidase-4 inhibitor (23) was recently demonstrated to achieve good glycemic control in *HNF1A*-MODY with reduced or no hypoglycemia, suggesting possible utility as a first-line *HNF1A*/*HNF4A*-diabetes treatment.

GCK encodes glucokinase, an enzyme catalyzing glucose phosphorylation at glycolysis initiation. GCK is a pancreatic β cell glucose sensor; genetic defects change the glucose-stimulated insulin secretion threshold (24, 25). In the United Kingdom, the prevalence of *GCK*-hyperglycemia was estimated at 0.1% among White Europeans (26) — higher than that of *HNF1A*-diabetes because the lack of symptoms keeps many cases from coming to medical attention. Further studies are needed in other populations. *GCK*-hyperglycemia has limited phenotypic heterogeneity; most patients have lifelong mild, persistent, and asymptomatic fasting hyperglycemia within the prediabetes range (27), with hemoglobin A_{1c} values not exceeding 7.5% (60 mmol/mol; ref. 28), though some have glucose levels that meet the diabetes mellitus (DM) criteria, and a few have T2D and related complications, likely due to additional genetic and environmental risk factors (29, 30). Glucose levels are resistant to lowering by insulin or oral agents. Moreover, since *GCK*-hyperglycemia does not appear to be associated with significant microvascular and macrovascular diabetes complications (14, 31), patients with *GCK*-hyperglycemia usually do not require glucose-lowering medication, except possibly during pregnancy. Maternal *GCK* mutations increase risk for macrosomia and associated perinatal complications similarly to gestational or pre-gestational diabetes of any type owing to the excess insulin secretion in response to a hyperglycemic intrauterine environment. Fetal *GCK* mutations decrease birthweight as a result of poor insulin response. A paternally inherited fetal mutation places the fetus at risk for low birthweight in a normoglycemic intrauterine environment. A maternal mutation creates a hyperglycemic intrauterine environment for fetal insulin secretion needed for normal growth of a GCK-deficient fetus, and thus attempts at normalizing maternal glucose may result in harm. In pregnant women with *GCK* mutations, it is recommended that, at minimum, fetal growth be monitored by serial ultrasound to guide treatment, but it is ideal to know the fetal mutation status early in pregnancy (32). A noninvasive technique for determining fetal *GCK* mutation status from cell-free DNA in maternal circulation is being developed that will enable women with a mutation-positive fetus to be discharged from high-risk antenatal care (33).

HNF1B variants are estimated to account for less than 1% of MODY (34). Patients with *HNF1B* defects may exhibit early-onset DM only; diabetes with renal, pancreas, or liver phenotypes (renal cysts and diabetes [RCAD] syndrome); or other features with or without diabetes, such as neurodevelopmental disorders (35, 36) and hypomagnesemia. *HNF1B* genotype-phenotype correlation is currently unclear, with clinical heterogeneity even among family members with the same variant. However, renal outcome as measured by estimated glomerular filtration rate has been reported to be better in deletion versus nondeletion variants (36, 37); this is hypothesized to result from a dominant-negative effect (38, 39). Some *HNF1B*-MODY initially responds to sulfonylurea or repaglinide (36) but may ultimately require insulin.

Rare MODY-classified monogenic diabetes types

ATP-sensitive potassium channel (K_{ATP} channel) diabetes. Pathogenic variants in *ABCC8* and *KCNJ11*, the genes encoding sulfonylurea receptor 1 (SUR1) and the inward rectifier potassium channel 11 (Kir6.2), subunits of the ATP-sensitive potassium channel (K_{ATP} channel) found in β cells (Figure 1), are common causes of NDM (either permanent or transient; see below) but also can occasionally cause diabetes with later childhood or young adult onset (sometimes referred to as MODY12 [ref. 40] and MODY13 [ref. 41], respectively). K_{ATP} diabetes is discussed further in the NDM section below.

The prominent and rarer types of MODY and their genetic and clinical features are summarized in Table 1. Emerging findings obtained through next-generation sequencing (NGS) to identify new causes of MODY have suggested potential roles of *APPL1* (42) and *PCBD1* (43) in MODY.

Neonatal DM

NDM is defined as diabetes diagnosed within the first 6 months of age and can be either permanent (PNDM) or transient (TNDM). Clinical features of NDM also include intrauterine growth retardation, failure to thrive, polyuria, and severe dehydration (44, 45). Depending on the genetic etiology, some patients can also have birth defects and neurological disorders (46). It affects 1 in 90,000 to 260,000 live births (47, 48), 50% being PNDM and 50% being TNDM (44).

The diabetes phenotype in TNDM results from inadequate insulin production presenting at the first week of life and resolving by 18 months (44), but 50% of patients relapse during early adulthood (46). Approximately 60%–70% of TNDM is caused by overexpression of paternally expressed imprinted genes on chromosome 6q24 (hereafter referred to as 6q24-TNDM) resulting from paternally inherited duplications or paternal disomy for the region or chromosome (both copies inherited from the father; ref. 49). The remaining cases mostly result from mutations in K_{ATP} channels, *KCNJ11* (50) and *ABCC8* (51), which tend to be functionally less severe than those causing PNDM (52). There are also

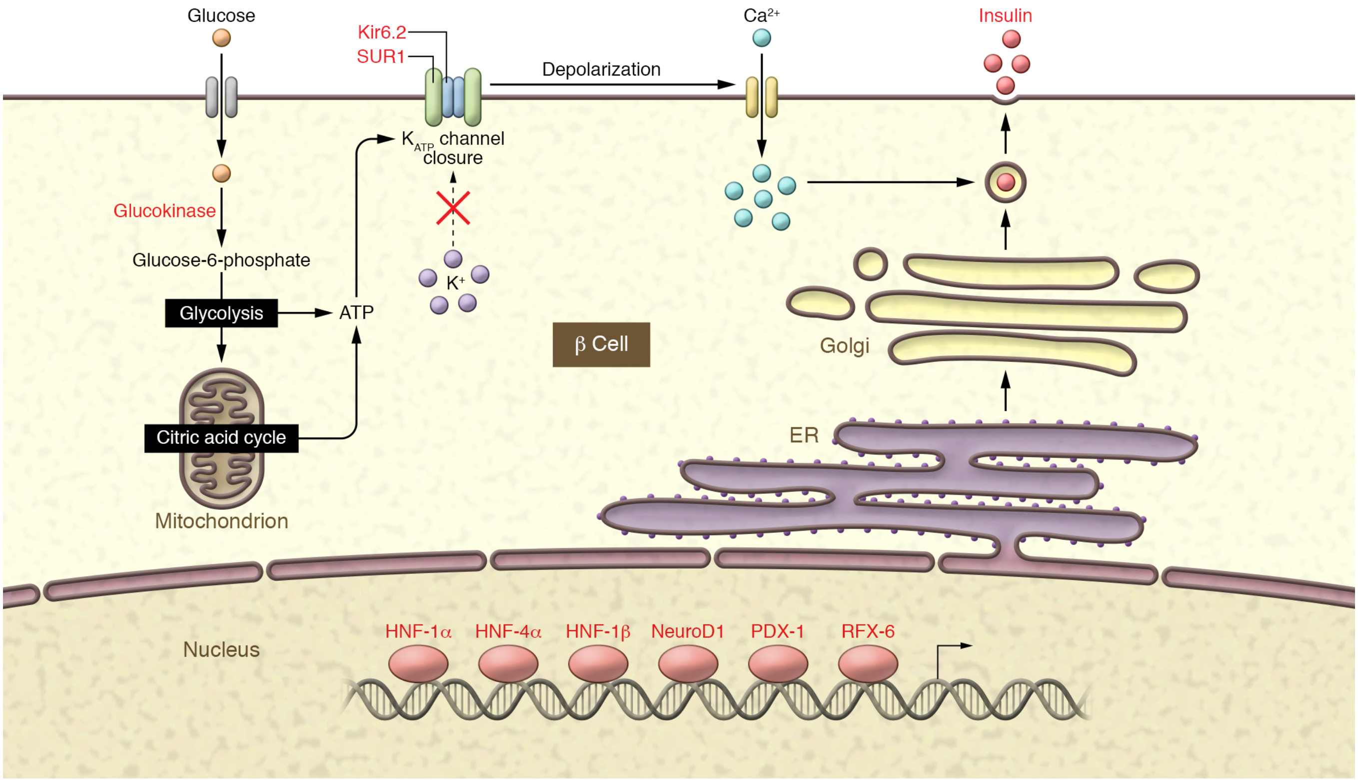

Figure 1. Schematic representation of glucose-induced insulin secretion and MODY-associated genes. The pancreatic K_{ATP} channel directly regulates insulin secretion. It is a hetero-octamer formed by four subunits of the inward rectifier potassium channel 11 (Kir6.2, encoded by *KCNJ11*) and four sulfonylurea receptor 1 (SUR1, encoded by *ABCC8*) subunits. Glucose enters the β cell and glucokinase phosphorylates glucose to glucose-6-phosphate, which further breaks down in the glycolysis and citric acid cycle to produce ATP. The increased ATP/MgATP ratio leads to the closure of the K_{ATP} channel and causes depolarization of the β cell membrane and subsequent activation of voltage-gated calcium channels. Calcium flows into the cell through activated voltage-gated calcium channel and triggers the insulin to be released from the β cell. Transcription factors (*HNF1A*, *HNF4A*, *HNF1B*, *NEUROD1*, *PDX1*, and *RFX6*) constitute a network that regulates the expression of insulin and β cell development and proliferation. The MODY-associated genes are labeled in red.

rare occurrences attributed to mutations in *INS* (encoding the insulin precursor molecule preproinsulin; refs. 51, 53, 54), *HNF1B* (55, 56), and other genes (Table 2). It remains undetermined why only some TNDM patients relapse later, but theories about β cell function and the development of insulin resistance at puberty represent possible explanations (57).

Some of the same genes implicated in TNDM, including *ABCC8*, *KCNJ11*, and *INS*, also have variants that more commonly cause PNDM. Homozygous or compound heterozygous inactivating *GCK* mutations cause PNDM (ref. 25 and Table 2). PNDM can also be part of IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, caused by variants in the *FOXP3* gene; Wolcott-Rallison syndrome, caused by variants in *EIF2AK3*; and others (58). Unlike more common types of PNDM, the PNDM of IPEX syndrome (and a few other rare types of monogenic diabetes; refs. 59, 60) is autoimmune, as FOXP3 is crucial in maintaining regulatory T cells' normal function of inhibiting proliferation and cytokine production of other T cells (61). PNDM in Wolcott-Rallison syndrome is possibly due to increased pancreatic β cell apoptosis that is regulated by *EIF2AK3* (62). Genes implicated in NDM and associated phenotypes are listed in Table 2. Since a genetic cause has been identified in only 82% of patients with NDM (63), the search continues through exome sequencing, most recently implicating *YIPF5* in autosomal recessive neonatal diabetes and microcephaly (64).

It is recommended that patients diagnosed with diabetes in the first 6 months of life obtain immediate genetic testing to identify the subtype, since T1D is extremely rare in this subgroup. Approximately 80%–85% of NDM cases have an identifiable genetic cause (63), half of these being K_{ATP}-diabetes caused by *KCNJ11* or *ABCC8* mutations, treatable with high-dose sulfonylureas rather than insulin (50, 65, 66). The benefit of identifying patients with K_{ATP}-diabetes is thus considerable, and many studies have attempted to establish genotype-phenotype correlation (67) to facilitate the prediction of patients' clinical courses based on genetic data.

NDM caused by pathogenic variants in K_{ATP} channels. Activating K_{ATP} channel gene variants cause NDM by decreasing ATP's ability to achieve channel closure in multiple ways (68). Whether variants will cause PNDM or TNDM (or, rarely, MODY) is determined in part by the functional severity of the mutation as well as which gene is involved, with *KCNJ11* variants mainly associated with PNDM and most *ABCC8* variants linked to TNDM (51, 69). Diabetes severity could be partially explained by the extent to which the variant impacts ATP sensitivity (70); however, the same variant in one family could cause both NDM and MODY in different patients (e.g., the *KCNJ11* C42R variant; ref. 71), suggesting that other mechanisms influence the development of clinical presentation. Loss-of-function (LOF) mutations in both genes cause an increase in insulin secretion and present as congenital hyperinsulinemic hypo-

Table 2. Genetic causes of neonatal diabetes with current ISPAD testing guidelines

Gene	Phenotype	Inheritance	Other features	Pathophysiology	Reference
ABCC8	PNDM, TNDM	AD	Developmental delay, epilepsy (DEND)	β Cell dysfunction	76, 153, 154
EIF2AK3	PNDM	AR	Wolcott-Rallison syndrome	β Cell destruction	62
FOXP3	IPEX	XLR	IPEX syndrome	β Cell destruction	61
GATA4	PNDM, TNDM	AD	Pancreatic agenesis, congenital cardiac defects, developmental delay, neurocognitive defects	Abnormal pancreatic development	155
GATA6	PNDM	AD	Pancreatic agenesis, congenital cardiac defects, congenital biliary tract anomalies	Abnormal pancreatic development	156, 157
GCK	PNDM	AR		β Cell dysfunction	25, 158–160
GLIS3	PNDM	AR	Congenital hypothyroidism, IUGR, polycystic kidney disease	Abnormal pancreatic development	161–163
HNF1B	PNDM, TNDM	AD	Pancreatic hypoplasia and renal cyst	Abnormal pancreatic development	55, 56
IER3IP1	PNDM	AR	Microcephaly, simplified gyral pattern, severe epilepsy	β Cell destruction	164
INS	PNDM, TNDM	AD, AR		β Cell destruction	53, 150–152, 166–170
KCNJ11	PNDM, TNDM	AD	Developmental delay, epilepsy (DEND)	β Cell dysfunction	76, 153, 154
MNX1	PNDM	AR	Developmental delay, sacral agenesis, imperforate anus, IUGR	Abnormal pancreatic development	170
NEUROD1	PNDM	AR	Developmental delay, cerebellar hypoplasia, sensorineural deafness, and visual impairment	β Cell dysfunction	145
NEUROG3	PNDM	AR	Malabsorptive diarrhea	Abnormal pancreatic development	171–173
NKX2-2	PNDM	AR	Developmental delay, hypotonia, short stature, deafness, constipation	Abnormal pancreatic development	170
PAX6	PNDM	AR	Brain anomalies, microphthalmia	Abnormal pancreatic development	174–176
PDX1	PNDM	AR	Pancreatic agenesis (common)	β Cell dysfunction	141, 142, 177–182
PLAGL1/ HYMAI	TNDM	Imprinting	Macroglossia, umbilical hernia	Abnormal pancreatic development	183
PTF1A	PNDM	AR	Pancreatic agenesis, cerebellar agenesis	Abnormal pancreatic development	184–186
RFX6	PNDM	AR	Pancreatic hypoplasia, intestinal atresia, and gallbladder aplasia or hypoplasia (Mitchell-Riley syndrome)	Abnormal pancreatic development	187–190
SLC2A2	PNDM	AR	Fanconi-Bickel syndrome	β Cell dysfunction	191
SLC19A2	PNDM	AR	Rogers syndrome	β Cell dysfunction	192
WFS1	PNDM	AD, AR	Wolfram syndrome	β Cell destruction	94, 95
ZFP57	TNDM	AR	IUGR, microglossia, facial dysmorphism, cardiac anomalies, umbilical hernia, and developmental delay	Abnormal pancreatic development	193

The Exeter Genomics Laboratory (Royal Devon and Exeter NHS Foundation Trust and University of Exeter Medical School, Exeter, United Kingdom) maintains an up-to-date, annotated list of genes sequenced for monogenic diabetes (Diabetes Genes website; https://www.diabetesgenes.org/tests-for-diabetes-subtypes), which currently includes 71 genes, including some with putative/research status, of which 35 have been evaluated for neonatal diabetes, including those listed here. In addition to MODY and NDM genes, the list also contains genes for syndromic subtypes diagnosed outside of the neonatal period. AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; PNDM, permanent neonatal DM; TNDM, transient neonatal DM; XLR, X-linked recessive.

glycemia when found in the homozygous or compound heterozygous state (72, 73) and when dominant LOF mutations are found in the heterozygous state. In addition, paternally inherited recessive LOF mutations in combination with somatic loss of maternal 11p15.5 chromosomal region cause focal hyperinsulinism (74).

K_{ATP}-NDM is autosomal-dominantly inherited but often (60%–84%) arises de novo (75, 76). Some individuals with NDM have neurological features in addition to DM (77), as K_{ATP} channels are expressed in other tissues, including muscle and brain. Common K_{ATP}-NDM features include muscle weakness, developmental delay, and early-onset epilepsy (DEND syndrome), while those with intermediate DEND (iDEND) syndrome do not have epilepsy (78). Treatment of K_{ATP}-NDM caused by either *KCNJ11* or *ABCC8* variants with high-dose sulfonylureas has proven safe and effective for both short-term and long-term glycemic control and may resolve CNS features (79–82). Ninety percent of K_{ATP}-NDM patients could switch from insulin therapy to sulfonylurea successfully (79, 83), with mutation severity (77, 84, 85) and diabetes duration before the transition (86) predicting the likelihood of success. For patients who cannot completely transfer to sulfonylurea, combining insulin and sulfonylurea has shown favorable results (87).

6q24-TNDM. Although patients with 6q24-TNDM always present with growth retardation and hyperglycemia during the neonatal period, different etiologies, including paternal uniparental disomy, partial duplication of paternal origin, or a methylation defect of maternal origin on 6q24, all lead to the overexpression of *PLAG1* and *HYMAI*, encoding a zinc finger protein (ZFP) and long noncoding RNA, respectively. In other cases, *ZFP57* variants cause hypomethylation of multiple imprinted loci, including at the 6q24 locus. The treatment for the first onset of diabetes is insulin, and many are treated with insulin during remission, while some are successfully treated with sulfonylureas or a combination of sulfonylureas and insulin (88, 89). Compared with K_{ATP}-TNDM patients, patients with 6q24-TNDM were observed to have lower birthweight and earlier presentation (90). Some patients with 6q24-TNDM may also experience hyperinsulinemic hypoglycemia following diabetes remission (91). Certain congenital abnormalities, such as macroglossia, are characteristic of 6q24-TNDM and thus could help to distinguish this type of TNDM from other types in considering testing strategies.

Syndromic diabetes

In addition to RCAD syndrome due to *HNF1B* variants as described above, other monogenic syndromes include DM as one of the clinical features. We describe the best-characterized of these syndromes below.

Wolfram syndrome. Two types of Wolfram syndrome (WS) corresponding to two causative genes have been identified to date. Wolfram syndrome 1 (WS1), characterized by diabetes insipidus, DM, optic atrophy, and deafness, is a rare autosomal recessive disease caused by variants in wolframin ER transmembrane glycoprotein (*WFS1*). Severe cases with dominant heterozygous variants are also reported (92). Often, patients' first manifestation is DM at an average age of 6 years. Though most WS1 patients require daily insulin as therapy, the high morbidity and mortality rates as well as low average age of death make an accurate and timely diagnosis essential. Recently, a presentation similar to WS1 in many *WFS1* mutation–negative patients was linked to variants in CDGSH iron sulfur domain 2 (*CISD2*) and thus named Wolfram syndrome 2 (WS2). Clinical features of WS2 resemble those of WS1 but without diabetes insipidus and with the addition of peptic ulcer bleeding and defective platelet aggregation (93). In addition, there are some *WFS1* mutations that cause isolated diabetes with significantly reduced penetrance or nonpenetrance for other WS-related features (94, 95).

Insulin resistance due to insulin receptor defects. Genetic defects in the insulin receptor gene (*INSR*) result in several insulin resistance syndromes, which are distinguished from typical insulin resistance not only by their severity but by normal lipid profiles because the etiology is directly due to defects in insulin receptor signaling rather than obesity and its sequelae (96). The most common type is type A insulin resistance syndrome, which has autosomal dominant and autosomal recessive forms. Type A insulin resistance syndrome affects predominantly nonobese females and presents with extreme insulin resistance, acanthosis nigricans, hirsutism, and polycystic ovarian disease (97, 98). Rabson-Mendenhall syndrome (RMS) is an intermediate form of insulin resistance with autosomal recessive inheritance. Patients with RMS have clinical features of extreme insulin resistance, acanthosis nigricans, hirsutism, dental precocity, thick nails, pineal hyperplasia, genital enlargement in both males and females, abdominal distension, and other distinctive dysmorphic features (99, 100). The most severe form is Donohue syndrome (DS), an autosomal recessive disorder in which patients present with failure to thrive, severe hyperinsulinemia, and fasting hypoglycemia. Patients with DS seldom survive infancy (101). LOF variants in the fibronectin type III (FnIII) domain are proposed to be associated with more severe DS, and there are genotype-phenotype and structure-phenotype correlations of *INSR* variants (102).

Lipodystrophy. Monogenic lipodystrophy is a group of diseases featuring a complete or partial lack of adipose tissue and adipose tissue–derived hormones, which results in insulin resistance and other metabolic complications. Unlike insulin receptor defects, the lack of adipose tissue in lipodystrophy leads to dyslipidemia and insulin resistance due to spillover of fat into ectopic areas, paradoxically similar to the consequences of obesity (96). Based on the loss of adipose tissue, this disease can be divided into congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPLD). CGL is an autosomal recessive disease; pathogenic variants in genes encoding 1-acylglycerol-3-phosphate *O*-acyltransferase 2 (*AGPAT2*) and Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*) account for most CGL cases, with rare cases being caused by pathogenic variants in *CAV1* and *PTRF*. CGL patients show common features, such as generalized lipodystrophy, muscular appearance, DM, and dyslipidemia; however, patients with pathogenic *BSCL2* variants display lower serum leptin levels than patients with pathogenic *AGPAT2* variants (103) but a higher rate of developing intellectual disability (104). The majority of FPLD cases are caused by pathogenic variants in lamin A/C (*LMNA*) or PPARγ (*PPARG*), and there are also other rarer forms caused by pathogenic variants in *PLIN1*, *AKT2*, *LIPE*, *CIDEC*, and *PCYT1A*. Body fat deficiency in FPLD is found on limbs, buttocks, and hips. Patients with pathogenic variants of either *LMNA* or *PPARG* appear to benefit similarly from leptin replacement therapy with metreleptin (105) in terms of improved glycemia and cardiometabolic outcomes.

Mitochondrial diabetes. Mitochondrial diabetes, also known as maternally inherited diabetes and deafness (MIDD), is caused by pathogenic variants in mitochondrial DNA, mostly tRNA variant m.3243A>G. Patients often present with diabetes in adulthood, but a greater proportion of mutated mitochondrial genomes in the affected tissues is associated with a younger age of diagnosis of diabetes in some studies (106). The hearing loss associated with m.3243A>G is bilateral, sensorineural, and progressive, typically preceding the diagnosis of diabetes (107, 108). Other clinical features such as macular pattern dystrophy, nephropathy, and neurological symptoms are more common in rarer forms of mitochondrial diabetes than the classical form (109). The penetrance of mitochondrial diabetes is estimated to be nearly 100% by the age of 70 years. The disease etiology determined that patients have impaired insulin secretion, and insulin treatment is eventually required for most patients. The effects of other treatments, such as coenzyme Q_{10} and PPARγ agonists, were only evaluated in single cases, thus requiring caution for application. To better screen patients suspected to have mitochondrial diabetes, clinical features including diabetes and hearing loss on the maternal side are key. Tian et al. established a mitochondrial diabetes score system with good performance (100% sensitivity, 69.9% specificity) to select patients diagnosed with T2D for genetic testing in a Chinese cohort (110), although this system needs validation in other populations.

Challenges in identifying and diagnosing monogenic diabetes

The broad application of personalized medicine to patients with monogenic diabetes faces challenges in two aspects: detecting patients suspected of having monogenic diabetes to pursue

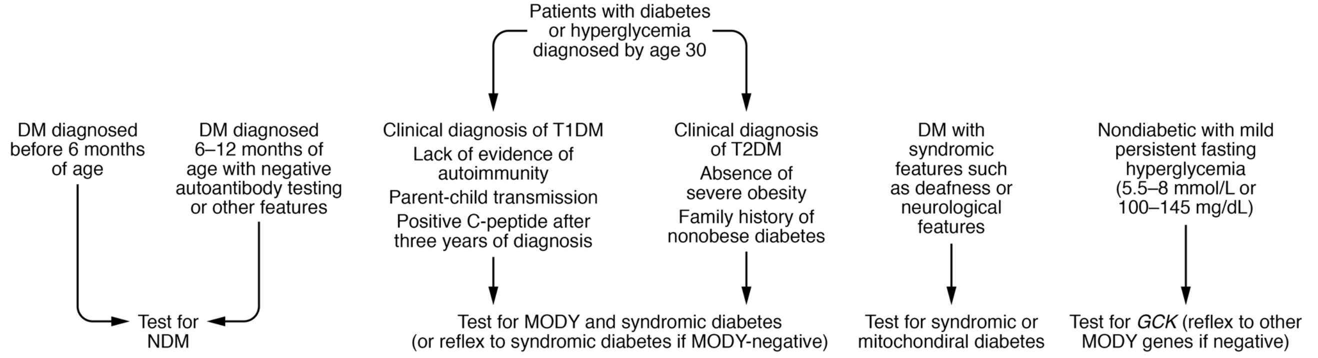

Figure 2. Proposed diagnostic algorithm for monogenic diabetes. Though the majority of patients diagnosed between 6 and 12 months have T1D, NDM can exist in these patients; genetic testing should be considered if they test negative for autoantibody, have extrapancreatic features, or have unusual family history (1, 2). High prevalence of MODY was observed in C-peptide–positive T2D diagnosed before 30 years regardless of metabolic syndrome status (116).

etiology-based therapies and accurately interpreting sequence variants of monogenic diabetes genes.

Monogenic diabetes detection methods

At present, practical guidelines for systematic screening for monogenic diabetes have been limited. The International Society for Pediatric and Adolescent Diabetes (ISPAD) has recommended testing for NDM in all patients diagnosed with diabetes before the age of 6 months as well as in patients diagnosed with diabetes before the age of 12 months with negative islet antibodies. This recommendation not only has the potential to dramatically improve care at the individual level when K_{ATP}-diabetes is diagnosed but has been shown to be cost-effective in this population (111). However, adult and pediatric T1D and T2D populations, which also include misdiagnosed patients with monogenic diabetes (112), are more challenging to screen routinely for MODY (111) and can be challenging especially for clinicians with limited experience diagnosing MODY. More complex screening criteria based on age of onset, family history, endogenous insulin secretion, nonobesity, and absence of pancreatic autoantibodies are needed to achieve cost-effectiveness and an ideal balance of sensitivity and specificity (113–115). The American Diabetes Association (ADA) recommends some scenarios for considering testing individuals who do not fit into the T1D or T2D classifications (2). A proposed algorithm to increase sensitivity is shown in Figure 2. Clinicians are referred to the primary source (116) as well as current ADA (2) and ISPAD guidelines (1) for further guidance; additional development is needed and is ongoing in this area.

Biomarkers or derived scores avoid reliance on clinical judgments and arbitrary cutoffs and establish a quantitative evaluation that could be validated and replicated across cohorts. The Swedish Better Diabetes Diagnosis (BDD) study showed that absence of glutamic acid decarboxylase (GAD), islet antigen-2, zinc transporter 8 antibodies, and insulin autoantibodies could be a good discriminator, since in this study, MODY patients were only identified from the antibody-negative group, and 15% of antibody-negative patients had MODY (115). However, other studies have shown that 1%–2% of patients diagnosed with MODY are GAD antibody positive (117), reducing the antibody's sensitivity as a screen. Meanwhile, the types of autoantibodies tested on each patient may vary depending on the clinic; thus, using negative antibodies as a screening method may not be practical without standardization. Table 3 summarizes published biomarkers other than pancreatic antibodies that have been utilized to distinguish monogenic diabetes subtypes from T1D or T2D. Limited by the low prevalence of monogenic diabetes, these biomarkers were developed in selected populations to differentiate the most common types of MODY.

In addition to biomarkers, Shields et al. established a MODY calculator predicting the possibility of testing positive for MODY given a set of common clinical criteria (118). In the initial cohort of White European patients who were diagnosed before the age of 35, the cutoff of probability at 40% yields sensitivity of 96% and specificity of 91% in differentiating MODY from T2D, and yields 87% sensitivity and 88% specificity for MODY versus T1D. Validations in other cohorts with different ethnic backgrounds show variable outcomes, suggesting room for improvement, including the need for a more ethnically diverse reference database.

Selection of method and genes for testing

Previously, molecular diagnosis of monogenic diabetes was usually performed through Sanger sequencing of one or several common-cause genes based on clinical suspicion. With the development of NGS, all known monogenic diabetes genes or even a patient's whole exome can be analyzed simultaneously. Targeted panels typically include all the MODY genes, or at least the most common ones, as well as the NDM and syndromic forms of diabetes genes. There are both advantages and disadvantages to using NGS gene panels. The low price of massively parallel sequencing enables the analysis of additional genes that were reported to be associated with syndromic forms of diabetes. This is useful because patients with syndromic forms of diabetes may lack or appear to lack the clinical features that would lead to testing of a single syndromic gene (119). However, it is important that diagnostic panels not include genes with weak or disputed associations with monogenic diabetes, or, if they are included for surveillance purposes, that they not be reported (120). The yields of these panels will not only facilitate molecular diagnosis but also add rare or novel variants to the knowledge base for future studies. Sanger confirmation is sometimes needed after variant discovery in NGS

Table 3. Biomarkers for monogenic diabetes detection

	Cutoff value	Differentiation	Sensitivity	Specificity	Reference
Standard biomarkers					
Fasting C-peptide	≥0.62 ng/mL	MODY vs. T1D in children and adolescents	93%	90%	194
Random or glucagon-stimulated C-peptide	≥0.2 nmol/L	*HNF1A*- and *HNF4A*-MODY vs. T1D in adults	100%	96%	116
Autoantibodies	GADA < 99th percentile	*HNF1A*-, *HNF4A*-, and *GCK*-MODY vs. T1D	99%	62%	117
	IA-2 < 99th percentile	*HNF1A*-, *HNF4A*-, and *GCK*-MODY vs. T1D	100%	57%	117
	GADA and IA-2 < 99th percentile	*HNF1A*-, *HNF4A*-, and *GCK*-MODY vs. T1D	99%	82%	117
	GADA and/or IA-2 and/or ZnT8A < 99th percentile	*HNF1A*-, *HNF4A*-, and *GCK*-MODY vs. not-known MODY in children	100%	88%	115
	GADA and/or IA-2 and/or ZnT8A and/or IAA < 99th percentile	*HNF1A*-, *HNF4A*-, and *GCK*-MODY vs. not-known MODY in children	100%	89%	115
Proposed biomarkers					
Serum 1,5-anhydroglucitol	>11 μg/mL	*GCK*-MODY vs. T2D	75%	75%	195
	>7.5 μg/mL	*GCK*-MODY vs. *HNF1A*-MODY	86%	84%	195
Highly sensitive C-reactive proteins (standard in UK)	≤0.5 mg/L	*HNF1A*-MODY vs. T2D	>74%	>68%	196
	≤0.75 mg/L	*HNF1A*-MODY vs. T2D	79%	71%	197
	≤0.75 mg/L	*HNF1A*-MODY vs. T1D	79%	67%	197
	≤0.4 mg/L	*HNF1A*-MODY vs. T2D	71%	77%	198
	≤0.28 mg/L	*GCK*-MODY vs. T1D	67%	68%	199
	≤0.2 mg/L	*HNF1A*-MODY vs. T1D	80%	80%	199
	≤0.185 mg/L	*HNF1A*-MODY vs. *GCK*-MODY	80%	75%	199
	≤0.81 mg/L	*HNF1A*-MODY vs. non–*HNF1A*-MODY young-adult-onset nonautoimmune diabetes	88%	69%	200
Urinary C-peptide/creatinine ratio	≥0.2 nmol/mmol	*HNF1A/4A*-MODY vs. T1D	97%	96%	201
	≤3.1 nmol/mmol	*HNF1A/4A* MODY vs. T2D	81%	44%	201
	≥0.22 nmol/mmol	MODY vs. T1D in children and adolescents	96%	86%	194
HDL-cholesterol	≤1.56 mM	*GCK*-MODY vs. T1D and HNF1A-MODY	86%	55%	202
Plasma glycan GP30	<0.7%	*HNF1A*-MODY vs. non–*HNF1A*-MODY young-adult-onset nonautoimmune diabetes	88%	80%	200

panels, though increasingly less so except in difficult regions of the genome. Regardless of methodology, it is becoming increasingly clear that evaluating only exonic regions will overlook some causal variants, as variants in the noncoding regulatory and deep intronic regions and 5′- and 3′-UTRs have also been implicated in monogenic diabetes (16, 121).

Searching for monogenic diabetes using exome or genome sequencing enables novel gene discovery and also requires caution. The coverage of exome sequencing may not be complete, leading to the risk of false negatives (122, 123). In addition, as exome or genome sequencing could discover variants that are potentially important to health or reproduction but are unrelated to the clinical indication, the reporting of such secondary findings must be addressed, with consideration of the recommendations of organizations such as the American College of Medical Genetics and Genomics (ACMG; ref. 124). With these caveats, this approach can serve as a powerful tool for searching for candidate genes in patients with monogenic diabetes for whom variants in known genes have not been found (125).

Variant classification

Key to diagnosing monogenic diabetes and other genetic conditions is not only identifying the variant but also distinguishing disease-causing variants from normal variation. Previous approaches to determine whether a variant identified in a patient was disease-causing involved sequencing a group of matched controls (usually 100–200 people) to assess the variant's presence in the general population. This approach was limited because the sample size was too small to rule out population prevalence being too high for the disease; e.g., *HNF1A*-diabetes has an estimated population prevalence of 1 in 10,000. Moreover, the extent to which rare but benign genetic variation existed in the population studied was not known and was thus probably underestimated. As NGS has begun to boom, the problem of large quantities of genetic data for interpretation has arisen for genetic diseases in general. The genetic and phenotypic heterogeneity of monogenic diabetes, and its overlapping features with T1D and T2D, together increase the difficulty of interpreting the pathogenicity of variants found in patients suspected to have monogenic diabetes. On the other hand, NGS emergence has led to the availability of exome and genome sequences of over 100,000 individuals of diverse ancestries in the gnomAD database, dramatically improving the ability to assess variant frequency in the general population. Additional resources have emerged, including computational predictive tools (126–128), and other sources of data, including phenotype specificity, familial segregation, and functional studies, are also used. However, there is subjectivity in assigning pathogenicity to variants, and in the early 2010s, a lack of consistency of variant interpretation across laboratories became apparent.

In 2015, the ACMG and the Association for Molecular Pathology (AMP) jointly published a consensus recommendation on standards and guidelines for clinical genomic variant interpretation (129). The guidelines were developed through data sharing by a large number of American Board of Medical Genetics and Genomics–certified clinical molecular geneticists and pathologists from Clinical Laboratory Improvement Amendment/College of American Pathologists–accredited laboratories. The recommendations suggested that variants could be assigned to a five-tier system of classification: (a) pathogenic, (b) likely pathogenic, (c) uncertain significance, (d) likely benign, or (e) benign. The proposed sets of criteria include population data, computational and predictive data, clinical data, functional data (in vitro studies), and pedigree segregation. Each criterion is weighted by different levels of strength based on observed evidence and combined with other collected criteria to reach a conclusion. Since the publication of the initial ACMG/AMP guidelines, additional refinements have been published to improve rigor, including recommendations for evaluating the strength of evidence for LOF (130), standards for assessing functional studies (131), and application of a Bayesian quantitative point system (132).

Value of establishing gene-specific rules

The aim of the ACMG/AMP guidelines is to provide a universal set of criteria for interpreting variants for Mendelian disease. Additionally, each gene-disease pair requires further specification to reflect the specific disease frequency, clinical features, and genotype-phenotype relationships. In 2013, the Clinical Genome (ClinGen) Resource was founded by the National Human Genome Research Institute to serve as a knowledge base that defines gene-disease relationships, curate variants of genetic disease using a standardized approach, and distribute information about the variants to researchers and clinicians. Since then, dozens of expert panels and working groups have been formed to examine specific gene or disease groups for determining clinical significance and constructing gene-specific standardizations. The Monogenic Diabetes Expert Panel (MDEP), established in 2017, brings together experts and data to adapt the ACMG/AMP variant interpretation guidelines for monogenic diabetes genes and classify variants using these gene-specific rules, thereby improving the accuracy of variant classification in these genes and in turn improving the ability to accurately diagnose monogenic diabetes (133).

Value of data sharing

The establishing of guidelines is fundamental to standardized and concordant interpretation of monogenic diabetes gene variants. This process calls for expertise in endocrinology, molecular genetic testing, genetic counseling, and biochemistry. To reach the full potential of precision medicine in monogenic diabetes, centralization of case-level data is important. For instance, when the variant being evaluated is not observed in the general population but is observed in affected individuals, a higher number of occurrences leads to a higher level of evidence supporting pathogenicity. However, the uncommonness of monogenic diabetes often makes it difficult for individual laboratories to acquire enough cases. By pooling case data, expert panels can achieve levels of case-based evidence for pathogenicity not possible for any single laboratory or clinic.

Value of functional evidence

Well-established functional studies on variants boost the understanding of disease mechanisms and provide evidence supporting or disputing the pathogenicity of the variants. Studies have shown that functional analyses clarify variant interpretation in *HNF1A*-MODY variants, especially when family segregation data or phenotype data are not available (134). Caution is needed in using these data, because not all functional assays reflect the disease mechanism and not all variants impact the function in the same way. Full inspection of the consequences of a variant may require multiple assays to reach a conclusion (135). Systematic validation and statistical quantification of the level of strength of pathogenicity or benignity in functional assays are recommended (131). This approach encourages high-throughput mutation screenings, such as saturation mutagenesis (136) and systematic functional profiling of variants identified in the population (137, 138), which consist of pathogenic and benign variants. The MDEP is currently developing standards for evaluating evidence from luciferase assays for transactivation, which assess transcriptional activity of *HNF1A* and *HNF4A* variants, along with assays of DNA binding activity and protein expression (138, 139). For *GCK* variants, similar work is focused on the relative activity index of glucokinase as a measure of enzyme kinetic characteristics (140). In the longer term, multiplexed assays of variant effect (MAVEs) could provide comprehensive catalogs of allelic effects that can be interrogated to aid variant interpretation. This approach is particularly well suited for transcription factors such as HNF1A. It is important to note that functional evidence does not singlehandedly implicate a variant in disease; the functional data must be evaluated in concert with the population and clinical data to make a pathogenicity determination.

Conclusion

Accurate genetic diagnosis of monogenic diabetes is crucial for patients, since it helps optimize treatment, especially for some patients switching from insulin or metformin to low-dose sulfonylureas (*HNF1A*-MODY and *HNF4A*-MODY) or no treatment (*GCK*-MODY) or from insulin to high-dose sulfonylureas (K_{ATP}-diabetes). Additionally, accurate monogenic diabetes diagnosis leads to better familial risk management and clinical course prediction. Advancement in genetic testing technology has increased the capacity of genetic diagnosis while decreasing sequencing cost. However, until we can offer genetic testing to every patient with diabetes, prioritizing patients with high suspicion of monogenic diabetes through assessment of their biomarker profiles or probability score is more practical. Monogenic diabetes provides an example of translating research findings into clinical practice that improves diagnosis and quality of life. Multidisciplinary expert collaboration and case sharing combined with incorporation of basic science into sequence variant interpretation will lead to improved diagnosis. Establishing clear guidelines for evaluating the causality of individual variants by this process is essential for widespread diagnosis of monogenic diabetes; more broadly, routine incorporation of emerging genomic data into the care of diabetes and disease in general is needed to realize the full potential of personalized and precision medicine. And as we celebrate the 100th anniversary of insulin's discovery, it seems fitting to now celebrate and disseminate our more recently discovered ability to identify individuals who can make their own insulin once they have received the appropriate genomic diagnosis and treatment.

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