



Monogenic diabetes: An evidence-based clinical approach

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Abstract

Monogenic diabetes is a heterogeneous disorder characterized by hyperglycemia arising from defects in a single gene. Maturity-onset diabetes of the young (MODY) is the most common type with 14 subtypes, each linked to specific mutations affecting insulin synthesis, secretion and glucose regulation. Common traits across MODY subtypes include early-onset diabetes, a family history of autosomal dominant diabetes, lack of features of insulin resistance, and absent islet cell autoimmunity. Many cases are misdiagnosed as type 1 and type 2 diabetes mellitus. Biomarkers and scoring systems can help identify candidates for genetic testing. GCK-MODY, a common subtype, manifests as mild hyperglycemia and doesn't require treatment except during pregnancy. In contrast, mutations in *HNF4A*, *HNF1A*, and *HNF1B* genes lead to progressive beta-cell failure and similar risks of complications as type 2 diabetes mellitus. Neonatal diabetes mellitus (NDM) is a rare form of monogenic diabetes that usually presents within the first six months. Half of the cases are lifelong, while others experience transient remission. Permanent NDM is most commonly due to activating mutations in genes encoding the adenosine triphosphate-sensitive potassium channel (*KCNJ11* or *ABCC8*) and can be transitioned to sulfonylurea after confirmation of diagnosis. Thus, in many cases, monogenic diabetes offers an opportunity to

provide precision treatment. The scope has broadened with next-generation sequencing (NGS) technologies, replacing older methods like Sanger sequencing. NGS can be for targeted gene panels, whole-exome sequencing (WES), or whole-genome sequencing. Targeted gene panels offer specific information efficiently, while WES provides comprehensive data but comes with bioinformatic challenges. The surge in testing has also led to an increase in variants of unknown significance (VUS). Deciding whether VUS is disease-causing or benign can be challenging. Computational models, functional studies, and clinical knowledge help to determine pathogenicity. Advances in genetic testing technologies offer hope for improved diagnosis and personalized treatment but also raise concerns about interpretation and ethics.

Key Words: Monogenic diabetes; Maturity-onset diabetes of the young; Neonatal diabetes; Mitochondrial diabetes; Insulin resistance syndrome; Monogenic autoimmune diabetes; Next-generation sequencing

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Core Tip: Monogenic diabetes is an uncommon form of diabetes caused by single gene mutations. Depending on the type of underlying gene mutation, the disease can present at any age with diverse clinical presentations. The diagnostic workup includes genetic testing and may involve tests like C-peptide assay and autoantibody screening to exclude other forms of diabetes. Next-generation sequencing technologies such as targeted gene panels focusing on known monogenic diabetes genes, and whole-exome sequencing that analyze the protein-coding regions of the genome are replacing older methods like Sanger sequencing. Pitfalls in workup can include misdiagnosis as type 1 or type 2 diabetes, leading to inappropriate treatment and potential complications. This evidence-based review updates the current clinical approach to monogenic diabetes.

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INTRODUCTION

Monogenic diabetes refers to a heterogeneous group of disorders characterized by diabetes mellitus arising from a defect in a single gene. Although the disease accounts for about 1%-2% of the global diabetes burden, only a small proportion receives the correct and timely diagnosis[1-3]. The two most common forms are maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus (NDM). However, several other subtypes are also described, developing from gene mutations affecting insulin resistance, autoimmunity, or mitochondrial function[4,5].

While many monogenic diabetes have distinct clinical features, others closely resemble type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM)[6-8]. An accurate diagnosis is essential for implementing precision treatment, monitoring disease progression, and providing genetic counseling[9,10]. Recent advancements and broader availability of genetic testing have increased the scope of diagnosis of monogenic diabetes[11,12]. This article aims to explore the best practices in diagnosing and treating monogenic diabetes, with a special focus on the latest scientific advancements, empowering clinicians to enhance outcomes.

LITERATURE SEARCH STRATEGY

A comprehensive literature search was conducted using PubMed, EMBASE, Scopus, Web of Science, Cochrane Library, and Google Scholar. A combination of Medical Subject Headings terms and free-text keywords were used, including "monogenic diabetes", "maturity-onset diabetes of the young", "neonatal diabetes", "monogenic autoimmune diabetes", "insulin resistance syndromes", "lipodystrophy", "mitochondrial diabetes" and "syndromic diabetes". The specific genetic subtypes such as "GCK-MODY", "HNF1A-MODY", "adenosine triphosphate-sensitive potassium (KATP) channel mutations", "ABCC8 mutations", "INS gene mutations" and other reported genetic mutations were also searched. Additional terms related to diagnosis and testing, such as "genetic testing", "molecular diagnosis", "next generation sequencing", "Sanger sequencing", "methylation analysis", "in silico analysis", "functional studies" and other related terms were included.

DISEASE SPECTRUM ACROSS DIFFERENT LIFE STAGES

Monogenic diabetes comprises a range of clinically, metabolically, and genetically diverse conditions caused by gene defects that affect insulin production, secretion, or action[4,5]. Table 1 outlines the different categories, including MODY, NDM, other monogenic forms with defective insulin synthesis and secretion, monogenic autoimmune diabetes syndromes, and monogenic insulin resistance syndromes. Figure 1 depicts a suggested approach to diagnosing monogenic diabetes mellitus based on the age of onset, islet antibody status, C-peptide levels, family history, and the presence or absence of extra-pancreatic features[4,8,13-31].

Monogenic diabetes presents at various stages of life, with specific types more likely at particular phases. Hyperglycemia during the first six months of life is primarily due to NDM. T1DM is the most probable differential diagnosis of diabetes in childhood, although MODY and syndromic causes can present during this time. Post-puberty, the prevalence of T2DM is on the rise, but MODY should be considered when the clinical picture is suggestive. In adulthood, MODY and mitochondrial diabetes are the alternate possibilities for T2DM. Common misdiagnoses can occur at each stage, highlighting the importance of age-specific differentials[5]. Figure 2 depicts the clinical and laboratory clues in the differential diagnosis of monogenic diabetes mellitus states at diverse life stages[5,32-35].

MODY

MODY is the prototypical form of monogenic diabetes, usually manifesting in individuals younger than 25 years with autosomal dominant inheritance. It has 14 known subtypes linked to gene mutations affecting insulin production and glucose regulation[16,19]. MODY types were initially classified numerically, but genetic defects associated with each subtype are currently used to subtype MODY[36]. The mutations involved in the pathogenesis of MODY and clinical features are enumerated in Table 2[16-19,30,37-62]. The subtypes differ in the age of onset, progression and complication rate, treatment response, and extra-pancreatic manifestations. The most common mutations are *HNF1A* (MODY3), *GCK* (MODY2), *HNF4A* (MODY1), and *HNF1B* (MODY5)[63].

Pathogenesis of MODY

The mutations in MODY affect transcription, glucose sensing, protein folding, ion channel function, and signal transduction[19]. Most gene mutations causing MODY, including *HNF4A*, *HNF1A*, and *HNF1B*, result in defects in transcriptional regulation. The hepatic nuclear factors are expressed in various tissues, including the liver, pancreas, and kidney[64]. The *HNF1A* gene is crucial for pancreatic β -cell development and function, regulating genes related to insulin synthesis, secretion, and glucose metabolism. Heterozygous mutations in *HNF1A* lead to progressive β -cell dysfunction, reduced insulin secretion in response to glucose, and a lower renal threshold for glucose[37,65]. Similarly, the *HNF4A* gene, along with transcription factors like *HNF1A* and *HNF1B*, regulate insulin gene expression and control genes involved in insulin secretion, glucose transport, and metabolism[19,20]. *HNF1B* is expressed during embryonic development in various tissues, including the kidney. Mutations in *HNF1B*, in addition to diabetes mellitus, also result in renal cysts, renal dysplasia, and urinary tract malformations[41]. The other transcription factors *PDX1*, *NEUROD1*, *KLF11*, *PAX4*, and *BLK* also play critical roles in β -cell development, insulin biosynthesis, and secretion[19].

Mutations in the *GCK* gene lead to altered glucose sensing, raising the threshold for glucose-stimulated insulin secretion. This results in mild, stable hyperglycemia without the risk of complications[39]. Carboxyl-ester lipase or *CEL*-MODY, characterized by endocrine and exocrine pancreatic insufficiency, occurs due to misfolding and cytotoxic aggregation of carboxyl-ester lipase[66]. Mutations in the *INS* gene are characterized by misfolding and intracellular accumulation of proinsulin, β -cell apoptosis, and progressive insulin secretory defect[67]. *ABCC8* and *KCNJ11* mutations represent ion channel disorders that are also responsible for NDM[68]. Lastly, the *APPL1* protein propagates the insulin signal within β -cells, and heterozygous loss-of-function mutations in this gene lead to defective glucose-stimulated insulin secretion and reduced survival of β -cells[69]. The genes affected in MODY and other monogenic diabetes are shown in Figure 3[4]. These genes are depicted based on their subcellular localization including the nucleus, endoplasmic reticulum, mitochondria, cytosol, islet cell plasma membrane, and insulin secretory granule.

Clinical features of MODY

Clinical manifestations can vary widely depending on the genetic mutation. However, some common unifying features are observed across different MODY subtypes. MODY should be suspected in individuals with early-onset diabetes, a family history of autosomal dominant diabetes, and in the absence of typical features of T1DM and T2DM[16,19].

T1DM is characterized by absolute dependence on insulin, low serum C-peptide and the presence of autoantibodies. Usually, a panel of five antibodies comprising glutamic acid decarboxylase-65, islet antigen 2, zinc transporter 8, islet cell and insulin antibodies are used for demonstrating autoimmunity in T1DM. The absence of the antibodies and presence of normal C-peptide in serum or urine in a child or young adult should raise doubts about the diagnosis of T1DM[5]. T2DM is increasingly being recognized in adolescents and young adults and is typically associated with features of insulin resistance.

The onset of MODY is typically before the age of 25 years, though mild fasting hyperglycemia in *GCK*-MODY is present since birth but remains asymptomatic[16,39]. The average age of diagnosis of *GCK*-MODY is 14 years, but can vary according to the population being studied and the diagnostic practices in place[70]. Individuals with *HNF1A* mutations, the commonest form of MODY in many countries, develop diabetes by 25 years in 63%, by 35 years in 79%, and by 55 years in 96%[38]. Those harboring truncating mutations manifest earlier with a median age of diagnosis at 18

Table 1 Various categories of monogenic diabetes with genes involved in the pathogenesis and the clinical features, with special emphasis on monogenic diabetes other than maturity-onset diabetes of the young and neonatal diabetes mellitus

Types	Subtypes/varieties	Gene/protein	Clinical features	Inheritance
MODY	MODY 1 to 14	See Table 2		See Table 2
Neonatal diabetes	Permanent NDM	See Table 2		See Table 2
	Transient NDM	See Table 2		See Table 2
Other monogenic diabetes with defective insulin synthesis and secretion	Mitochondrial DM	m.3243A > G	Maternally inherited diabetes and deafness	Maternal
	Wolfram syndrome 1 or 2	<i>WFS1</i> or <i>CISD2</i>	DIDMOAD 1 or 2 diabetes insipidus, diabetes mellitus, optic atrophy and deafness	AR
	Rogers syndrome	<i>SLC19A2</i>	Thiamine-responsive megaloblastic anaemia, deafness, and diabetes	AR
	H or PHID syndrome	<i>SLC29A3</i>	H syndrome: Hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomaly, hearing loss, low height, hypogonadism and hyperglycaemia; PHID syndrome	AR
Monogenic autoimmune diabetes syndromes	IPEX syndrome	<i>FOXP3</i>	IPEX syndrome	XR
		<i>LRBA</i>	Common variable immunodeficiency 8	AR
		<i>STAT3</i>	Infancy-onset multi-system autoimmune disease type 1	AD
	APECED syndrome	<i>AIRE</i>	Autoimmune polyendocrinopathy syndrome type 1	AR
		<i>IL2RA</i>	Immunodeficiency 41 with lymphoproliferation and autoimmunity	AR
	IPEX-like syndrome	<i>STAT1</i>	IPEX-like syndrome	AD
		<i>STAT5B</i>	Growth defect, primary immunodeficiency, and endocrine abnormalities	AR
Insulin resistance syndromes	Congenital generalized lipodystrophy (Seip-Berardinelli syndrome)	<i>AGPAT2</i>	CGL1-acromegalic features	AR
		<i>BSCL2</i>	CGL2-cardiomyopathy, polyneuropathy, mental retardation	AR
		<i>CAV1</i>	CGL3-short stature, pulmonary arterial hypertension, and vitamin D resistance	AR
		<i>PTRF</i>	CGL4-congenital myopathy, pyloric stenosis, cardiomyopathy, atlantoaxial instability	AR
	Partial lipodystrophy	<i>LMNA</i>	FPLD2-fat loss from limbs; fat deposition in face, neck and perineum (Dunnigan variety)	AD
		<i>PPARG</i>	FPLD3-loss of subcutaneous fat from distal extremities	AD
		<i>PLIN1</i>	FPLD4-loss of subcutaneous fat from extremities	AD
		<i>AKT2</i>	AKT2 linked FPLD-loss of subcutaneous fat from extremities	AD
		<i>CIDEA</i>	FPLD5-fat loss of lower limbs and abdomen, and multilocular lipid droplets	AR
		<i>LIPE</i>	FPLD6-upper body pseudo-lipomatosis, fat loss from limbs, and muscle atrophy in some cases	AR
		<i>LMNA</i>	Mandibuloacral dysplasia A syndrome-skeletal anomaly, loss of extremity fat, neuropathy, premature ageing	AR
		<i>ZMPST24</i>	Mandibuloacral dysplasia B syndrome-skeletal anomaly, loss of fat, premature	AR

		renal failure, progeroid	
<i>PIK3R1</i>	SHORT syndrome		AD
<i>POLD1</i>	MDPL syndrome		<i>De novo</i>
<i>WRN</i>	Werner syndrome-progeria and cataract		AR

MODY: Maturity-onset diabetes of the young; DM: Diabetes mellitus; NDM: Neonatal diabetes mellitus; IPEX syndrome: Immuno-dysregulation, polyendocrinopathy, enteropathy, X-linked; PHID: Pigmented hypertrichosis and insulin-dependent diabetes mellitus; APECED: Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; DIDMOAD: Diabetes insipidus, diabetes mellitus, optic atrophy and deafness; AD: Autosomal dominant; AR: Autosomal recessive; XR: X-linked recessive; CGL: Congenital generalized lipodystrophy; FPLD: Familial partial lipodystrophy; SHORT: Short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay; MDPL: Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome.

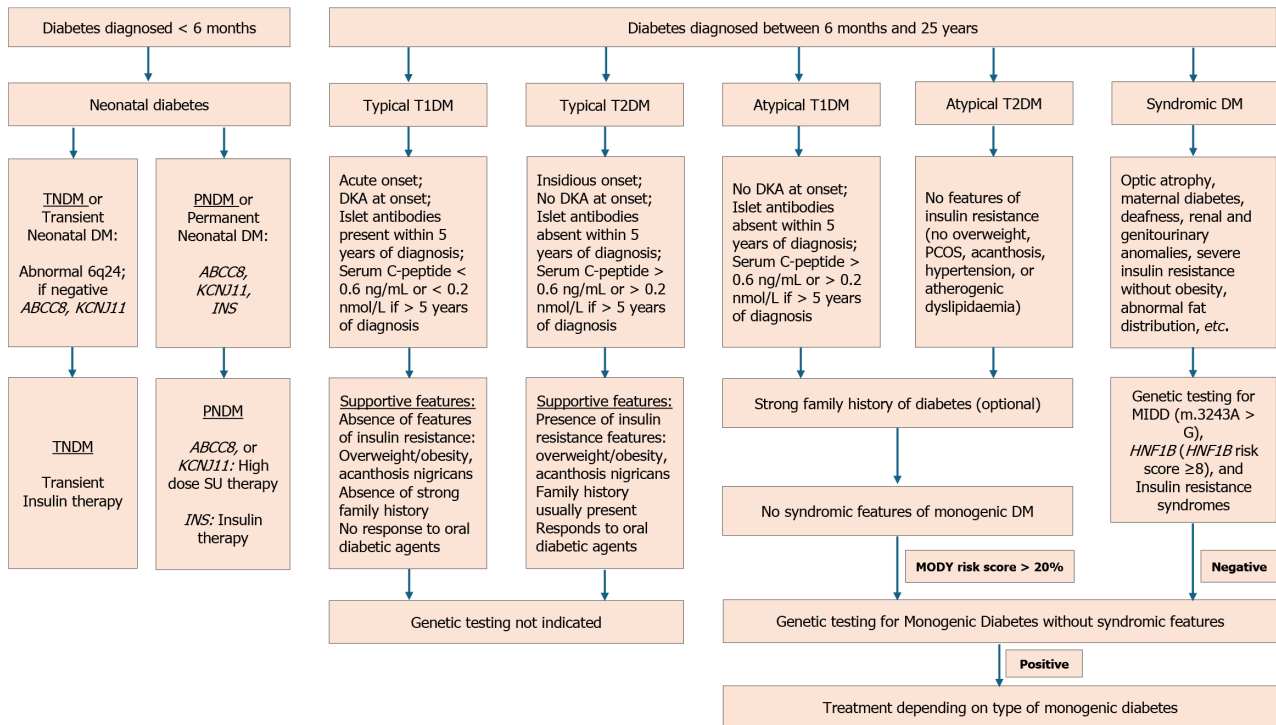


Figure 1 Approach to correctly diagnose youth-onset diabetes. DM: Diabetes mellitus; NDM: Neonatal diabetes mellitus; TNDM: Transient neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; SU: Sulfonylurea; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; DKA: Diabetic ketoacidosis; PCOS: Polycystic ovary syndrome; MODY: Maturity-onset diabetes of the young; MIDD: Maternally inherited diabetes and deafness.

years, compared to those having missense mutations whose median age was 22 years[71]. According to a multinational registry from four European countries, the median age of diagnosis is 13.8 years for *HNF4A*-MODY and 13.5 years for *HNF1B*-MODY[42].

A strong family history is usually evident, but that is often the case with T2DM, highlighting the need for genetic testing[72]. Though individuals with MODY have normal body mass index (BMI) or are only mildly overweight, 4% of youth with obesity or overweight with presumed T2DM have mutations for MODY[73]. *GCK*-MODY is characterized by mild fasting hyperglycemia and does not require treatment except during gestation[39]. Mutations in *HNF4A*, *HNF1A*, and *HNF1B* genes manifest as progressive β -cell failure, with a risk of macrovascular as well as microvascular complications similar to T2DM[38,41,65]. Certain subtypes have specific characteristics such as renal developmental disease or cysts in *HNF1B*-MODY, macrosomia and/or neonatal hypoglycemia mostly in *HNF4A*-MODY and rarely in *HNF1A*-MODY, and exocrine pancreatic dysfunction or pancreatic cysts in *CEL*-MODY[19,74-76].

Diagnostic approach

The clinical profile initially raises suspicion of MODY, which can be corroborated by biomarkers. Confirmation requires genetic testing. Detailed information should be obtained, including family history spanning three or more generations, the age and habitus at diagnosis, insulin dependence, response to medications used, and hypoglycemia history. Figure 4 represents the diagnostic algorithm for the three common MODY variants with onset of diabetes below 25 years, a strong family history of diabetes, and the presence of clinical features, biomarkers, and response to treatment.

Table 2 Various types of maturity-onset diabetes of the young and neonatal diabetes mellitus with the genes involved in the pathogenesis and the clinical features

	Subtype	Gene	Frequency	Gene-disease	Clinical feature	Inheritance
MODY	MODY 1	<i>HNF4A</i>	14%	Classical MODY	Fetal macrosomia and/or neonatal hypoglycemia, respond to low-dose SU initially, progressive β -cell failure, require insulin later, risks of complications	AD
	MODY 2	<i>GCK</i>	22%		Mild fasting hyperglycemia does not require treatment except during gestation determined by the <i>GCK</i> mutation status of the foetus	AD, rarely AR
	MODY 3	<i>HNF1A</i>	33%		Disproportionate glucosuria (low renal threshold), response to low-dose SU initially, progressive β -cell failure, require insulin later, risks of complications	AD, rarely AR
	MODY 4	<i>IPF1/PDX1</i>	< 1%		A heterozygous mutation causing MODY or T2DM or homozygous mutation causing PNDM (see below)	AD
	MODY 5	<i>HNF1B</i>	6%	Syndromic MODY	Renal cysts and diabetes, pancreas hypoplasia, exocrine insufficiency, β -cell defect, low magnesium, gout, altered LFT, and autism; Require insulin; Risks of complications; 40% are <i>de novo</i>	AD
	MODY 6	<i>NEUROD1</i>	1%	Classical MODY	A heterozygous mutation causing MODY or homozygous mutation causing NDM (not mentioned below)	AD
	MODY 7	<i>KLF11</i>	< 1%	Evidence refuted	Potentially causing T2DM in the presence of obesity rather than causing MODY	AD
	MODY 8	<i>CEL</i>	< 1%	Syndromic MODY	Diabetes and pancreatic exocrine dysfunction; Pancreatic cysts may be present	AD
	MODY 9	<i>PAX4</i>	< 1%	Evidence refuted	Potentially causing T2DM in the presence of obesity rather than causing MODY	AD
	MODY 10	<i>INS</i>	2%	Classical MODY	Mild defects can present as MODY whereas severe defects can present as TNDM or PNDM (as below), insulin treatment preserves β -cell mass and insulin secretion	AD
	MODY 11	<i>BLK</i>	< 1%	Evidence refuted	Potentially causing T2DM in the presence of obesity rather than causing MODY	AD
	MODY 12	<i>ABCC8</i>	4%	Classical MODY	Manifest as relapse following TNDM or as isolated MODY with no history of TNDM, respond to low-dose SU	AD
	MODY 13	<i>KCNJ11</i>	2%		Manifest as relapse following TNDM or as isolated MODY with no history of TNDM, respond to low-dose SU	AD
	MODY 14	<i>APPL1</i>	< 1%	Evidence weak	Delayed onset MODY with low penetrance and less severity; Potentially causing T2DM in the presence of obesity rather than causing MODY	AD
	RFX6-MODY	<i>RFX6</i>	< 1%	Classical MODY	Significantly low penetrance; Likely to respond to DPP4 inhibitors or GLP-1 receptor agonists (low GIP levels are present in these patients)	AD
NDM	TNDM 45% NDM	<i>ZAC</i> and <i>HYMAI</i>	70% TNDM	TNDM1	6q24 abnormal uniparental disomy 40%, paternal duplication 40%, maternal hypomethylation 20%, macroglossia, umbilical hernia, cardiac/renal defect, hypothyroidism	Sporadic or AD
		<i>ABCC8</i>	15% TNDM	TNDM2	TNDM (early infancy), remission (early childhood), and/or relapse of diabetes (in adulthood), mild developmental features may be seen, marked response to low-dose SU	Sporadic or AD

	<i>KCNJ11</i>	10% TNDM	TNDM (early infancy), remission (early childhood), and/or relapse of diabetes (in adulthood), mild developmental features may be seen, marked response to low-dose SU	Sporadic or AD
	<i>INS</i>	5% TNDM	IUGR; Doesn't respond to SU but responds to insulin therapy	AD, rarely AR
	<i>HNF1B</i>		Renal cyst and pancreatic hypoplasia	AD
	<i>SLC2A2</i>		TNDM, PNDM (rare), or Fanconi-Bickel syndrome (Fanconi syndrome, short stature, rickets, growth retardation, hepatomegaly, and glucose/galactose intolerance)	AR
PNDM 45% NDM	<i>KCNJ11</i>	50% PNDM	DEND (developmental delay, epilepsy, NDM) or iDEND syndrome (mild developmental delay, no epilepsy), severe hyperglycemia, DKA frequent, response to high-dose SU	Sporadic or AD
	<i>INS</i>	30% PNDM	IUGR; Doesn't respond to SU but responds to insulin therapy	AD
	<i>ABCC8</i>	15% PNDM	DEND (developmental delay, epilepsy, NDM) or iDEND syndrome (mild developmental delay, no epilepsy), severe hyperglycemia, DKA frequent, response to high-dose SU	Sporadic, AD or AR
	<i>GCK</i>	3% PNDM	IUGR; Homozygous mutations causing PNDM requiring lifelong insulin therapy	AR
Syndromic NDM; 10% NDM	<i>IPF1/PDX1</i>	2% PNDM	Pancreatic hypoplasia causing PNDM (homozygous mutation)	AR
	<i>HNF1B</i>		Renal cyst and pancreatic hypoplasia	AD
	<i>EIF2AK3</i>	Rare	PNDM with spondyloepiphyseal dysplasia, and renal anomalies (Wolcott-Rallison syndrome)	AR
	<i>FOXP3</i>		IPEX syndrome	XR
	<i>GATA4/6</i>		Permanent neonatal diabetes with pancreatic agenesis and congenital heart defects	AD
	<i>RFX6</i>		Neonatal diabetes, pancreatic hypoplasia, gallbladder agenesis, intestinal atresia (Mitchell-Riley syndrome)	AR
	<i>GLIS3</i>		Congenital hypothyroidism, glaucoma, hepatic fibrosis, polycystic kidneys, developmental delay	AR
	<i>PTF1A</i>		Pancreatic and cerebellar hypoplasia	AR

MODY: Maturity-onset diabetes of the young; NDM: Neonatal diabetes mellitus; TNDM: Transient neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; AD: Autosomal dominant; AR: Autosomal recessive; XR: X-linked recessive; SU: Sulfonylurea; LFT: Liver function test; T2DM: Type 2 diabetes mellitus; DPP4: Dipeptidyl peptidase-4; GLP: Glucagon-like peptide; IUGR: Intrauterine growth restriction; DEND: Developmental delay, epilepsy, neonatal diabetes mellitus; iDEND: Intermediate developmental delay, epilepsy, and neonatal diabetes syndrome; DKA: Diabetic ketoacidosis; IPEX syndrome: Immuno-dysregulation, polyendocrinopathy, enteropathy, X-linked.

Biomarkers

While several biomarkers have been explored as diagnostic adjuncts, their clinical utility is limited. The wider availability of genetic testing *via* next-generation sequencing (NGS) has reduced the reliance on biomarkers. At best, biomarkers can be considered a supportive tool to guide the need for genetic analysis in resource-limited settings.

High-sensitivity C-reactive protein: A few studies suggest that high-sensitivity C-reactive protein (hs-CRP) levels are lower in *HNF1A*-MODY compared to other types of diabetes[77,78]. Deactivating mutations in *HNF1A* could result in reduced hs-CRP levels, given the presence of *HNF1A* binding sites in the promoter region of the CRP gene[79]. Other studies found an overlap in hs-CRP levels between *HNF1A*-MODY and different types of diabetes, suggesting that its role as a biomarker could be limited[80,81].

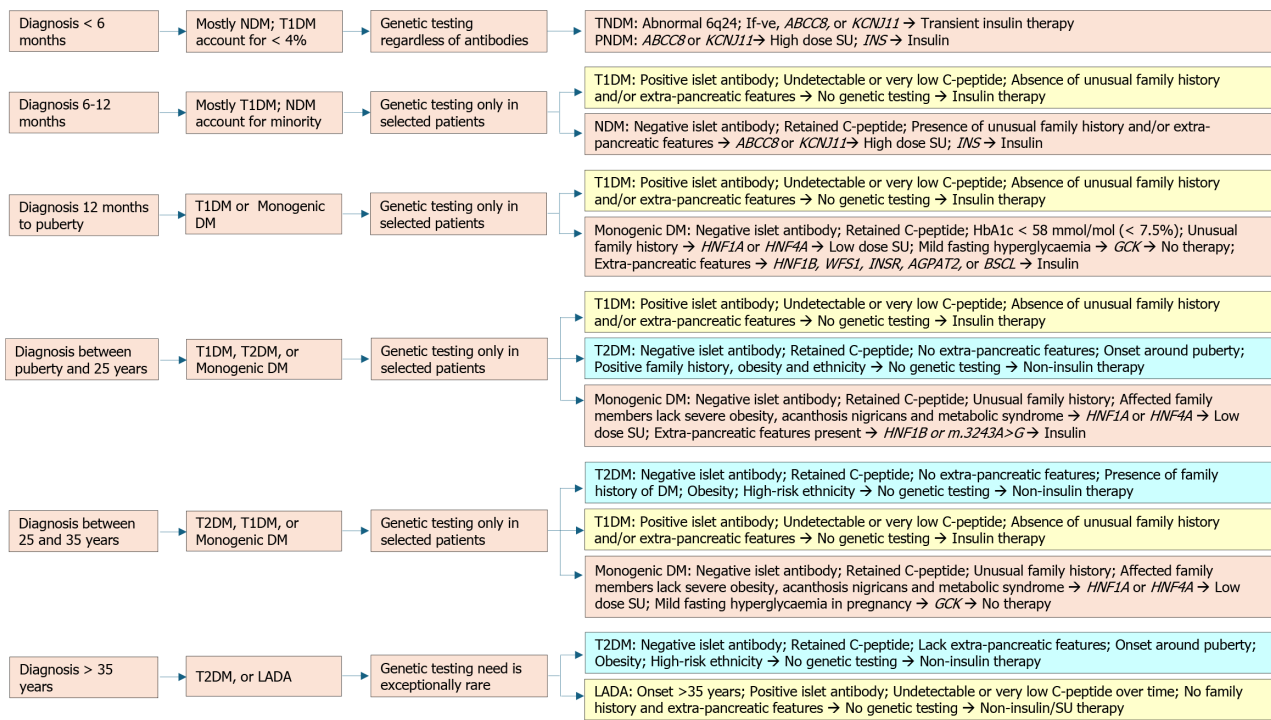


Figure 2 Clinical and laboratory clues in the differential diagnosis of monogenic diabetes mellitus state at diverse life stages. DM: Diabetes mellitus; NDM: Neonatal diabetes mellitus; TNDM: Transient neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; SU: Sulfonylurea; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; LADA: Latent autoimmune diabetes in adults; SU: Sulfonylurea; HbA1c: Glycated hemoglobin.

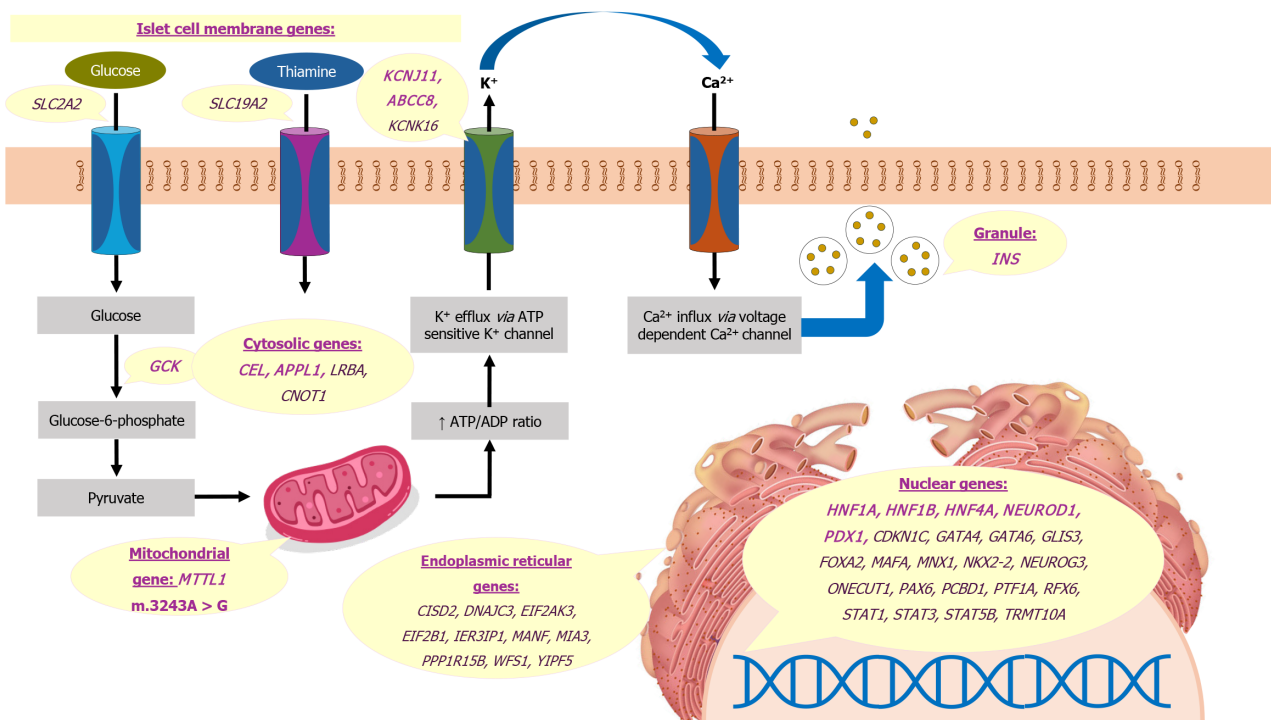


Figure 3 The genes that are affected in maturity-onset diabetes of the young and other monogenic forms of diabetes. K⁺: Potassium; Ca²⁺: Calcium; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate.

The hs-CRP assays used in a study from the United Kingdom and Croatia employed a wide-range latex-enhanced immunoturbidometric assay on an ADVIA 2400 analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany) with a quantification limit of 0.01 mg/L and Abbott hs-CRP method with a quantification limit of 0.1 mg/L, respectively. Both methods had a reproducibility coefficient of variation below 10.5% [82]. Platforms in another large multi-center European study included ADVIA 2400 analyzer (Siemens Healthcare Diagnostics, Frimley, United Kingdom), Konelab 60i analyzer (Thermo Fisher Scientific, Vantaa, Finland) and BN ProSpec analyzer (Siemens Healthcare Diagnostics, Erlangen,

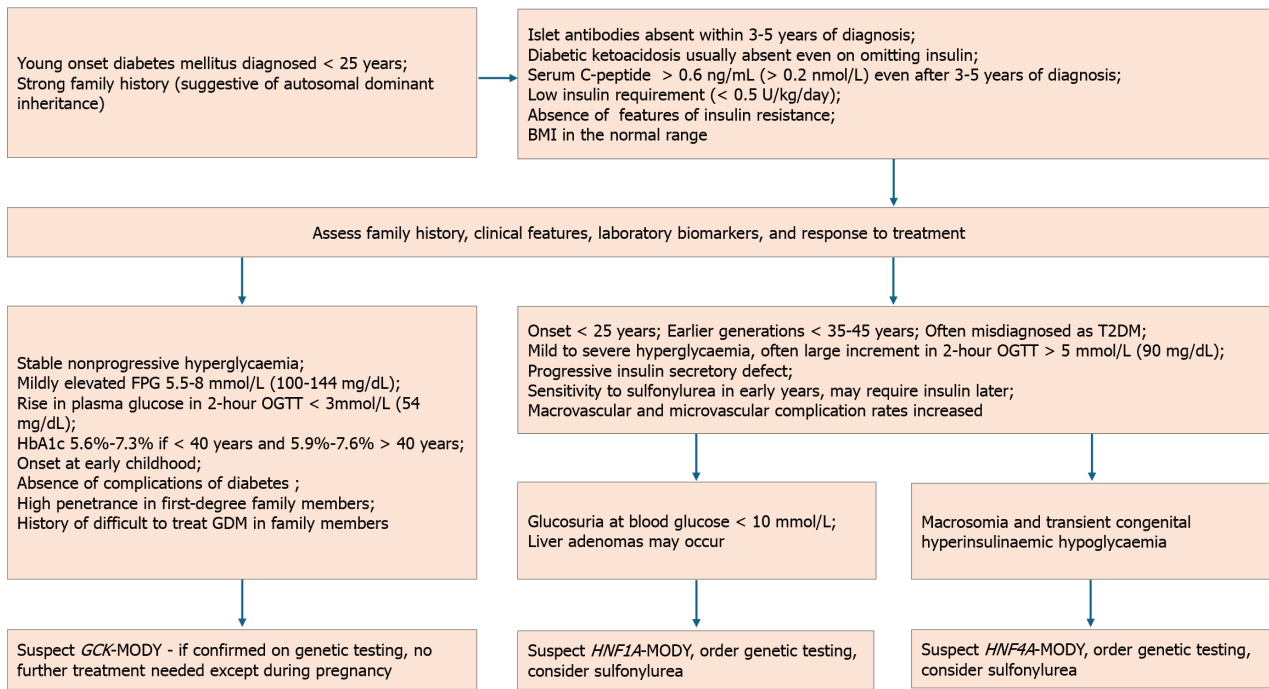


Figure 4 The diagnostic algorithm for the three common variants of maturity-onset diabetes of the young. FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test; HbA1c: Glycated hemoglobin; GDM: Gestational diabetes mellitus; MODY: Maturity-onset diabetes of the young; BMI: Body mass index; T2DM: Type 2 diabetes mellitus.

Germany), with lower limits of detection of 0.03 mg/L, 0.25 mg/L and 0.16 mg/L respectively. Criteria combining low hsCRP (≤ 0.25 mg/L for the first assay and ≤ 0.5 mg/L for the second two assays) and the age of diagnosis ≤ 25 years resulted in 90% sensitivity for detection of *HNF1A*-MODY with specificity ranging from 65% to 81% across assays. The authors noted that despite the statistically significant differences, the findings were not relevant practically for diagnostic purposes[83].

Glycosuria: *HNF1A*-MODY can be associated with defects in the promoter region of sodium-glucose cotransporter 2 (SGLT2) and demonstrates a low renal threshold because of decreased transporter expression[84]. Disproportionate glycosuria is present in 30%-40% of the cases of *HNF1A*-MODY, and the presence of glycosuria at blood glucose < 10 mmol/L (180 mg/dL) could serve as an indicator of this MODY subtype[37,85]. However, the studies have been heterogeneous and used both quantitative tests[85,86] and qualitative assessments utilizing dipstick[87].

Apolipoproteins and high-density lipoproteins: *HNF1A* and *HNF4A* genes play key roles in the transcription of proteins regulating apolipoprotein and high-density lipoprotein (HDL) levels[37,88]. HDL levels are elevated in *HNF1A*-MODY compared to T2DM[37,89]. Individuals with *HNF4A* mutations, on the other hand, have reduced HDL-cholesterol, apolipoprotein A1, apolipoprotein A2, and triglyceride, while low-density lipoprotein-cholesterol can be raised[40,90].

Studies from the United Kingdom and Croatia revealed higher HDL-cholesterol among individuals with *HNF1A*-MODY. Those with the mutations had a median HDL-cholesterol of 1.33 mmol/L (interquartile range 0.51), compared to 1.15 mmol/L (interquartile range 0.40) in those without the mutations[82]. Additionally, individuals with *HNF1A*-MODY had lower plasma triglycerides (1.36 mmol/L *vs* 1.93 mmol/L, $P = 0.07$) than those with T2DM. HDL-cholesterol above 1.12 mmol/L was 75% sensitive and 64% specific in differentiating *HNF1A*-MODY from T2DM[89].

The HDL assay platforms used in different studies include an automatic biochemical analyzer (AU5800; Beckman Coulter Inc., Brea, CA, United States)[91] and Architect ci4100 device (Abbott Diagnostics, Wiesbaden, Germany)[92]. The number of participants in most studies was less than 50 to 70[91,93] with only one series with more than 500 participants [89]. There is currently insufficient evidence to consider HDL as a biomarker for MODY.

Urinary C-peptide creatinine ratio: In adults with diabetes for over five years, a 2-hour post-meal (largest meal) urinary C-peptide creatinine ratio (UCPCR) ≥ 0.2 nmol/mmol differentiated *HNF1A*-MODY or *HNF4A*-MODY from T1DM with 97% sensitivity and 96% specificity. Urinary C-peptide was measured by electrochemiluminescence immunoassay on a Roche Diagnostics (Mannheim, Germany) E170 analyzer. UCPCR was predictable and lower in T1DM than *HNF1A*/*HNF4A* MODY [median (interquartile range)] [< 0.02 nmol/mmol (< 0.02 nmol/mmol to < 0.02 nmol/mmol) *vs* 1.72 nmol/mmol (0.98-2.90 nmol/mmol)][94]. With current available evidence, UCPCR can't be recommended to distinguish between monogenic diabetes and T2DM[95].

Other biomarkers: Other proposed biomarkers for *HNF1A*-MODY include fucosylated GP30 plasma glycans[80], microRNA-244[96], ghrelin[97], apolipoprotein M[98], and response to sulfonylurea[37,99]. Though the biomarkers can be a valuable clue, none can reliably diagnose MODY or distinguish between its subtypes. Genetic testing through NGS

offers high throughput, low cost, and accurate diagnosis of monogenic diabetes and is recommended in suspected cases of MODY.

MODY risk calculator and other MODY risk scores

Several risk calculators have been developed to identify individuals who may have MODY based on clinical and laboratory features. One such calculator is the MODY risk calculator (MRC) developed and validated by the University of Exeter group for GCK-MODY, HNF1A-MODY, and HNF4A-MODY in 1 to 35-year-old Caucasians. It can be accessed online at <https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator> and can assess the need for genetic testing in suspected cases[100]. MRC incorporates various factors such as gender, age at diabetes diagnosis, BMI, treatment history (diet, oral hypoglycemic agents, or insulin), glycosylated hemoglobin (HbA1c), family history of diabetes, ethnicity, and specific clinical characteristics. While initially validated for Caucasians, studies from China[101], Portugal [102], Australia[103], and Brazil[104,105] have found it to be applicable across different populations. In non-white populations, the probability is likely to be lower due to the higher prevalence of youth-onset T2DM[100]. The eight parameters used in the logistic regression model distinguished the three common monogenic diabetes subtypes collectively from T1DM or T2DM with a c-statistic of 0.98 and 0.95, respectively, in the Caucasian population[36].

The HNF1A-MODY clinical screening strategy utilizes four biomarkers: BMI < 28 kg/m², hs-CRP < 0.75 mg/L, fasting insulin < 102 pmol/L, and HDL-cholesterol > 1.12 mmol/L. In a Chinese population with young-onset diabetes, meeting three of the four criteria resulted in a sensitivity of 90.5% and specificity of 73.6% for identifying HNF1A-MODY. A sensitivity of 88.9% and specificity of 89.6% were attained when all four criteria were present[106]. However, this score has not been validated in other ethnicities. The authors did not specify the laboratory method used for insulin analysis in this study. The wide variability of commercially available insulin assays must be considered when interpreting results using different platforms.

The HNF1B score is calculated using 17 items, including factors such as antenatal discovery, family history, structural and pathological involvement of the kidneys, electrolyte or uric acid abnormalities (hypomagnesemia, hypokalemia, and early onset of gout), as well as the involvement of the pancreas, genital tract, and liver. The optimal cut-off threshold to exclude HNF1B mutations was 8, resulting in a sensitivity of 98.2%, specificity of 41.1%, and negative predictive value of 99%[107].

Management and prognosis of common types of MODY

HNF1A-MODY: HNF1A-MODY can lead to microvascular complications like retinopathy, nephropathy, and neuropathy, underscoring the importance of early diagnosis and treatment[108]. The phenotype of HNF1A-MODY ranges from mild nonprogressive hyperglycemia to progressive hyperglycemia and extra-pancreatic features[109]. Dietary management is often sufficient in individuals with mild hyperglycemia, while pharmacological interventions are necessary in progressive cases[5,63,110]. A randomized crossover trial demonstrated high sensitivity to oral sulfonylureas compared to metformin[111]. Decreased hepatic clearance of sulfonylurea derivatives, leading to increased serum levels and improved drug efficacy, probably increases the response to the drug[112].

International Society for Pediatric and Adolescent Diabetes guidelines recommend low-dose formulations like 20-40 mg/day gliclazide as the first-line therapy due to superior glycemic control and minimal risk of treatment failure[5]. In an observational study, many initially presumed T1DM cases could be shifted from insulin to sulfonylurea after HNF1A-MODY was diagnosed. Shorter diabetes duration, lower HbA1c, and normal or low BMI improve the chance of successful transition. For those with diabetes > 11 years and poor glycemic control, sulfonylurea can be considered as an adjunct to insulin rather than a replacement, especially in the presence of overweight or obesity[113].

Other treatment options include meglitinides, dipeptidyl peptidase-4 inhibitors[114], and glucagon-like peptide-1 receptor agonists[115]. In a randomized controlled trial from Denmark, the combination of glimepiride and linagliptin did not improve the mean amplitude of glycemic excursions (mean difference of -0.7 mmol/L, $P = 0.1540$) compared to glimepiride alone. However, reductions in the coefficient of variation on continuous glucose monitoring (-3.6%, $P = 0.0401$), HbA1c (-0.5%, $P = 0.0048$), and the dose of glimepiride (-0.7 mg/day, $P = 0.0099$) were demonstrated[114].

The safety of SGLT2 inhibitors in HNF1A-MODY remains unclear. Severe insulin deficiency, reduced expression of SGLT2 in the proximal tubules, and glycosuria cast doubts on the safety and efficacy of SGLT2 inhibitors[110,116]. Caution should be exerted, as diabetic ketoacidosis (DKA) has been reported in two HNF1A-MODY patients with the use of SGLT2 inhibitors[117].

HNF4A-MODY: Individuals with HNF4A-MODY typically exhibit normal glucose tolerance in the first or second decade but experience a gradual decline in insulin secretion after that. Complication rates are akin to those seen in T1DM and T2DM[40]. Sulfonylurea is the recommended treatment when lifestyle adjustments are insufficient. To avoid hypoglycemia, the initial dose is one-quarter of the typical starting dose for adults, with subsequent adjustment depending on blood glucose levels[63]. The sensitivity to secretagogues demonstrated in individuals with HNF4A-MODY may be slightly lower than that observed with HNF1A-MODY[72]. Most will require insulin later on in life as β -cell dysfunction progresses[118].

GCK-MODY: Individuals with GCK-MODY do not require pharmacological agents to control the mild nonprogressive fasting hyperglycemia other than during pregnancy[5,39]. Women are often misdiagnosed as gestational diabetes mellitus (GDM). In pregnancies with a known GCK-MODY mutation, treatment recommendations are based on the fetal genotype and growth[72]. If the mother has a heterozygous GCK mutation but the fetus has a normal genotype, insulin treatment is necessary to prevent fetal macrosomia. Conversely, if the fetus is affected by GCK-MODY, treatment is not

required. In the absence of fetal genotyping facilities, starting serial ultrasounds from 26 weeks onward is recommended. If the fetal abdominal circumference exceeds the 75th percentile, it indicates the absence of the fetal GCK mutation. Insulin is needed to prevent macrosomia in such situations. The insulin dosage required to achieve normoglycemia is higher than in GDM[119,120]. The algorithm for managing GCK-MODY in pregnancy is given in Figure 5[120-123].

NDM

NDM is a rare condition affecting 1:300000-400000 live births[17]. All infants diagnosed under 6 months should undergo genetic testing for a monogenic cause, regardless of their islet autoantibody status[5]. While T1DM is rare before 6 months, it can still occur in 4% of cases[124]. Some instances of NDM may be diagnosed between 6 and 12 months, although most infants in this age group have T1DM[51,125]. Reasons for considering genetic testing between 6-12 months include negative autoantibody results, extra-pancreatic features like gastrointestinal anomalies or congenital defects, unusual family history, or the development of multiple autoimmune disorders[5].

Pathogenesis of NDM

NDM is a diverse group of diseases with several reported genetic alterations. It can be attributed to two main groups of mechanisms: Malformation of the pancreas, which affects the development or survival of insulin-secreting cells, or abnormal functioning of the existing pancreatic β -cells[17,18]. In a series of 174 index cases of NDM, 47 had no detectable genetic defect, 40 (23%) had 6q24 abnormalities, 43 (25%) had mutations in *KCNJ11*, 31 (21%) had mutations in *ABCC8*, and 13 (7.4%) had mutations in *INS*[126]. About half of NDM cases require lifelong treatment and are classified as permanent NDM (PNDM)[126]. In contrast, transient NDM (TNDM) cases experience remission within a few weeks or months, though it may recur later in life[18,51,125].

Pathogenesis of PNDM

PNDM is a rare form of diabetes that typically manifests during infancy, with around 90% of cases appearing within the first six months of life[126]. The majority of infants with PNDM carry activating mutations in either of the two genes encoding the KATP channel (*KCNJ11* or *ABCC8*) or the *INS* gene. The mode of inheritance is autosomal dominant for mutations of *KCNJ11*, autosomal dominant or autosomal recessive for mutations of *ABCC8* and *INS*, and autosomal recessive for mutations of *GCK* and *PDX1*[52].

Activating mutations in *KCNJ11* or *ABCC8*, which code for the inner subunit (Kir6.2) and the outer subunit (sulfonylurea receptor 1), respectively, prevent KATP channel closure. The resultant hyperpolarized membrane state prevents calcium channel activation and insulin secretion[53,127]. KATP NDM typically presents in the first month of life as excessive urination, thirst, poor growth, dehydration, ketosis, and developmental delays[68,127]. The median age at diagnosis of PNDM is 9.6 weeks[128]. DKA was reported in 85% of cases[127]. Around one-fifth of children with *KCNJ11* mutations exhibit neurological symptoms from affection of KATP channels expressed in neurons and muscles. Severe mutations may result in the triad of developmental delay, early-onset epilepsy, and NDM, while milder mutations lead to less severe developmental disorders without epilepsy[129]. Intrauterine growth restriction (IUGR) is present in most cases and relates to decreased fetal insulin release[18]. Dominant heterozygous mutations in *INS* are the next common cause of NDM. Neurological manifestations are usually absent. Presentation can be delayed in some cases and can occur after 6 months.

NDM, due to *INS* gene mutation, should be managed with insulin[54,130]. Most children with activating mutations in the KATP channel genes can be switched from insulin to sulfonylurea tablets or suspensions. Treatment with sulfonylurea stabilizes glycemic control, carries minimal risk of hypoglycemia, and benefits neurological manifestations [131,132].

Pathogenesis of TNDM

The insulin output deficit in TNDM may stem from delayed maturation of pancreatic islets and β -cells due to altered gene expression on chromosome 6. Overexpression of the chromosome region 6q24 is the primary cause of TNDM1, the most common subtype of TNDM[133,134]. The region houses two major TNDM gene candidates, *ZAC* (zinc finger, apoptosis, and cell cycle) and *HYMA1* [(Fe) hydrogenase subunit HymA][135,136]. Normally, the 6q24 locus is imprinted, allowing only paternal allele expression, but in 6q24-TNDM, in about 70% of cases, loss of imprinting and consequent overexpression of both genes occur[55]. The overexpression can arise from paternal uniparental disomy of chromosome 6, duplication of the TNDM1 region of the paternal chromosome 6, or maternal hypomethylation of the TNDM1 region[17]. The rest of the cases of TNDM involve mutations in *KCNJ11* and *ABCC8* genes encoding the KATP channel and rarely *HNF1B* gene mutations[17,137-139].

The infant typically presents in the first few weeks after birth. Neonates harboring 6q24 mutations are diagnosed at a median age of one week. The presentation in those with KATP mutations occurs slightly later, at around 4 weeks[140]. DKA is less common compared to PNDM, but IUGR is more frequent[53]. Remission occurs before 4 months, but 70% of cases recur within the second decade[125,141]. Patients with a 6q24 locus abnormality may have developmental defects such as macroglossia, umbilical hernia, cardiac, renal, and urinary malformations, nonautoimmune anemia, hypothyroidism, and neurological disorders[126,142,143]. Initial stabilization requires insulin, but infants carrying mutations in the KATP gene can be shifted to sulfonylurea[5].

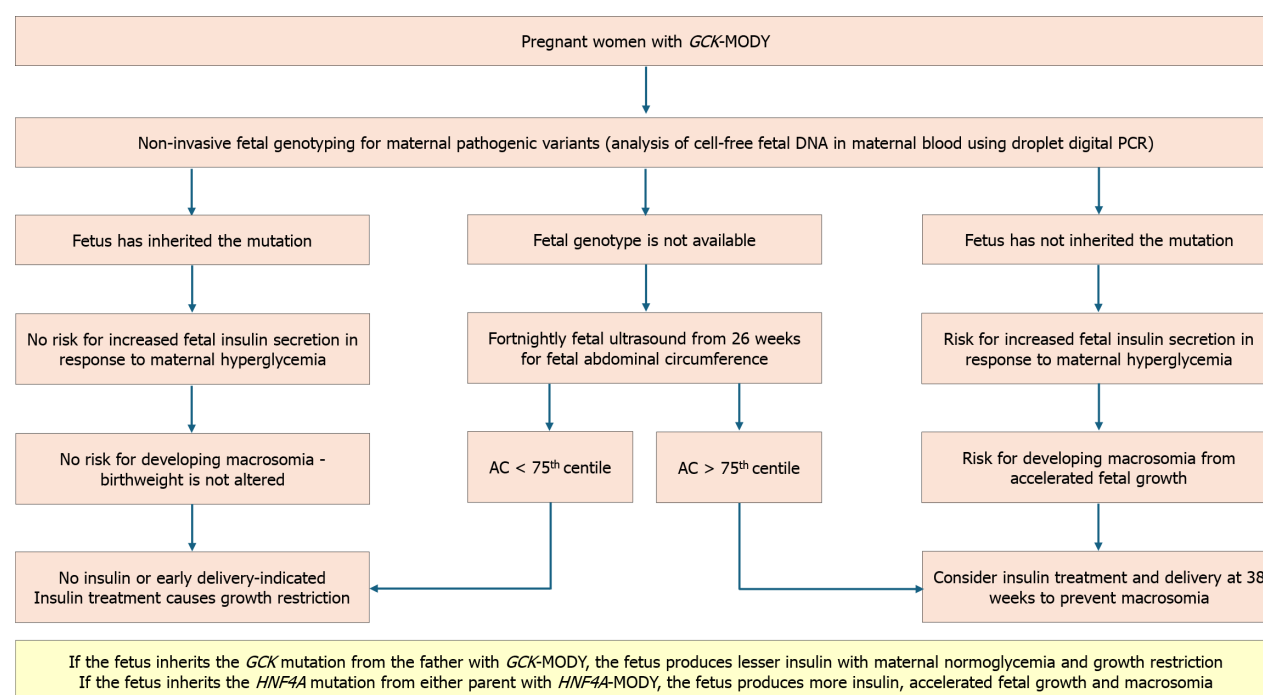


Figure 5 An algorithm for the management of *GCK*-maturity-onset diabetes of the young during pregnancy. AC: Abdominal circumference; PCR: Polymerase chain reaction; MODY: Maturity-onset diabetes of the young.

Monogenic autoimmune diabetes

Mutations in many genes (see Table 1) have been linked to autoimmune syndromes leading to diabetes in infancy with pancreatic islet autoantibodies[5,144]. These monogenic conditions, akin to pediatric T1DM, have been considered rare among early infancy T1DM cases[4,145]. Mutations in the *FOXP3* gene are responsible for immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome[29]. Other gene mutations like *CTLA4*, *ITCH*, *IL2RA*, and *LRBA* also cause autoimmune conditions with diabetes, enteropathy, hypothyroidism, and hemolytic anemia[146-149].

OTHER MONOGENIC FORMS OF DIABETES

Several rare forms of monogenic diabetes have been described, including insulin resistance syndromes, mitochondrial diabetes, and syndromic forms. Three syndromes of monogenic insulin resistance are Donohue syndrome (leprechaunism), Rabson-Mendenhall syndrome, and insulin resistance syndrome type A[27].

Monogenic lipodystrophy is associated with diabetes and results from the complete or partial absence of adipose tissues. Monogenic lipodystrophy is classified into two main types: Congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPLD). CGL, often caused by *AGPAT2* or *BSCL2* gene mutations, shows generalized fat loss along with diabetes and dyslipidemia. FPLD results from *LMNA* or *PPARG* mutations and presents as fat loss in specific areas like limbs. Leptin replacement therapy, like metreleptin, benefits individuals with FPLD and CGL, improving glycemia and cardiometabolic outcomes[25,26].

The presence of diabetes and multi-organ involvement, especially early-onset deafness with a maternal inheritance pattern, should raise the suspicion of a mitochondrial disorder. Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, and maternally inherited diabetes and deafness are the primary mitochondrial diabetes disorders, often attributed to the m.3243A > G mutation[21,150]. Mitochondrial diabetes typically manifests in adulthood, with earlier onset occurring in the presence of a higher proportion of mutated mitochondrial genomes[151]. The clinical details of the different forms of monogenic diabetes are summarized in Table 2.

GENETIC TESTS

Genetic screening for monogenic diabetes has been transformed by NGS technologies, replacing labor-intensive and costly methods like Sanger sequencing[152]. NGS encompasses two primary approaches: Targeted gene panels focusing on known monogenic diabetes genes and whole-exome sequencing (WES) analyzing the protein-coding regions of the genome[153]. Targeted gene panels are efficient and provide specific information. In contrast, WES offers comprehensive data, albeit with bioinformatics challenges[154-156].

Candidates for genetic testing

Given the unfeasibility of universal genetic screening for all cases of youth-onset diabetes, a combination of phenotypic and biochemical variables offers the best method to identify candidates for genetic testing[4]. A MRC to identify candidates for genetic screening has been validated in different ethnic groups[102-105]. However, the effectiveness of these criteria is questionable in populations with a high prevalence of youth-onset T2DM, like in South Asia. Additionally, South Asians often develop T2DM in the absence of features of insulin resistance, such as obesity or acanthosis[157]. Besides, the heterogeneity of different forms of monogenic diabetes underscores the need for tailored criteria to screen for different types of the disorder. We summarize the best practice methods for identifying candidates for genetic screening for the common forms of monogenic diabetes in Figure 6[52,150,154].

Techniques for genetic testing

NGS: Targeted gene panels using NGS are the preferred technique for confirming the diagnosis of monogenic diabetes [9]. Owing to their targeted nature, they rapidly and cost-effectively provide specific information with a lower risk of secondary information and data complexity[11,158]. While targeted gene panels require periodic redesign and validation as new genes are identified, WES doesn't have this limitation. However, WES generates large datasets that can be challenging to analyze, but it also allows for the discovery of pathogenic variants in genes not initially considered. Effective use of WES contributes to ongoing research and identifying new monogenic diabetes genes[9,52,159,160]. Several large series have confirmed the clinical utility of NGS for diagnosing MODY and other forms of monogenic diabetes[161-163].

Detection of copy number variations: Multiplex ligation-dependent probe amplification (MLPA) is used for detecting copy number variations (CNVs) such as deletions or duplications of one or more exons seen in *HNF1B*-MODY, *GCK*-MODY, or in mitochondrial diabetes with m.3243A > G mutation[9,164-166]. Conventionally, NGS cannot detect CNVs. However, CNV calling, a new bioinformatic tool, can assess CNVs using NGS output data without requiring additional sequencing[9,167]. MODY occurring due to CNVs in *GCK* and *HNF1B* have been detected by this technique[168,169]. A quantitative method based on pyrosequencing to analyze the heteroplasmy of m.3243A > G has been demonstrated to be accurate and reliable[170].

Sanger sequencing: Sanger sequencing, though largely replaced by NGS, remains an accurate and reliable method for detecting point mutations, small insertions/deletions (indels), and known variants. It is especially valuable for confirming specific genetic variants identified by other methods or for targeted sequencing of particular genomic regions. Sanger sequencing complements NGS technologies by providing confirmatory sequencing, resolving complex variants, and characterizing specific genomic regions with precision[9,12].

Detection of hypomethylation: The diagnosis of 6q24-TNDM may require a demonstration of relative hypomethylation within the 6q24 differentially methylated region by DNA methylation analysis. Southern blot, methylation-specific-MLPA, or methylation-specific polymerase chain reaction can confirm hypomethylation. DNA methylation studies can diagnose 6q24-TNDM caused by any genetic defect but don't establish a specific mechanism[171,172].

Challenges in diagnostic approach

Diagnosing monogenic diabetes presents several challenges. The limited awareness about this condition among healthcare providers can result in underdiagnosis or misdiagnosis in many parts of the world[7]. In the United Kingdom, several initiatives, including the genetic diabetes nurse project, the MODY probability calculator, and targeted NGS, have improved the detection of MODY by threefold over 10 years[173].

The clinical and genetic heterogeneity of monogenic diabetes, along with its overlap with common T1DM and T2DM, makes it challenging to distinguish based solely on clinical criteria[74]. The presence of mosaic patterns occasionally confounds the diagnostic process[9]. Not all individuals with pathogenic variants develop the disease because of the reduced penetrance and variable expressivity. Additionally, a wide range of symptoms and age of onset in those who manifest the disease can further complicate the diagnosis. Furthermore, *GCK*-MODY and T2DM can sometimes co-exist, complicating the management[174]. Understanding the genetic modifiers that influence penetrance and expressivity can reveal protective genetic variants, offering insights into more common forms of diabetes and potential new therapeutic strategies.

Genetic testing for MODY relies heavily on the depth and coverage of sequencing. Sequence depth refers to the number of times a nucleotide is read during the sequencing process, and higher depth increases the confidence in detecting variants, especially those that are rare or occur at low frequencies. Coverage, on the other hand, pertains to the proportion of the target region (in this case, the MODY genes) that is successfully sequenced. Comprehensive coverage ensures that all potential mutations within the MODY genes are identified. For accurate diagnosis and differentiation between MODY subtypes, as well as between MODY and other forms of diabetes like T2DM, both high sequence depth and extensive coverage are critical. Insufficient depth or coverage could lead to missed mutations or false-negative results, undermining the reliability of genetic testing[159,175].

Another challenge in clinical practice is negative genetic test results in a person with a strong clinical phenotype of MODY. It's important to re-evaluate the clinical diagnosis to ensure it aligns with MODY characteristics. Reassessing laboratory and clinical data, such as C-peptide levels and antibody testing, alongside a detailed family history, is crucial. Further genetic testing in cases with high probability, including comprehensive panels, such as WES or whole genome sequencing, may be necessary. Additionally, techniques like MLPA should be used to check for large deletions or duplications. Seeking expert consultation from specialists in monogenic diabetes or geneticists can provide valuable insights.

Longitudinal follow-ups to monitor the individual over time and enrolling them in research or clinical trials for advanced diagnostics can aid in accurate diagnosis[12,176].

Confirming the pathogenicity of a variant

NGS has revolutionized genetic testing for monogenic diabetes, making it more accessible and cost-effective. NGS has expanded the reach of diagnosis, including those with other single-gene disorders. However, with increased testing, there's also a rise in variants of unknown significance (VUS). These variants pose a challenge in distinguishing disease-causing mutations from harmless genetic variations[177].

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology published a consensus statement outlining recommendations for the interpretation of sequence variants. The statement suggested using standardized terminology like 'pathogenic', 'likely pathogenic', 'uncertain significance', 'likely benign', and 'benign' based on population data, computational analyses, functional studies, and segregation patterns to define variants [178].

National Institutes of Health-funded resources like ClinGen and ClinVar curate and publicize evidence on gene-disease and gene-variant relationships and refine practice guidelines periodically[179]. The formation of expert panels like the ClinGen Monogenic Diabetes Gene Curation Expert Panel and the Monogenic Diabetes Variant Curation Expert Panel represents a significant step in establishing guidelines and standards for determining the causative genes and variants in monogenic diabetes[180,181]. Assessment of variant pathogenicity in exome-based sequencing is complex and relies on computational models, *in vitro* analyses, and clinical information[182].

In silico models: In silico models for monogenic diabetes are computational tools used to simulate genetic processes and interactions associated with disease mutations. These models can help predict the effects of genetic variants on protein structure, function, and overall disease phenotype. They incorporate data from various sources, such as genomic sequences, protein databases, and functional assays, to provide insights into the pathogenicity of specific genetic variants and their contribution to disease development[178,183-185].

Functional studies: Functional studies help to assess the pathogenicity of genetic variants. These studies examine if the genetic variants impact the protein structure, function, and cellular processes related to glucose metabolism and insulin physiology. Both *in vitro* and *in vivo* models, including cell lines, patient-derived induced pluripotent stem cells (iPSCs), and animal models (*e.g.*, knockout or transgenic mice) have been employed. *In vitro* assays using β -cell lines or iPSC-derived β -like cells help assess the effect of specific mutations on insulin secretion, ion channel activity, and gene expression. Animal models provide insights into the systemic effects of mutations, such as glucose intolerance and beta-cell mass regulation. Advanced techniques like CRISPR-Cas9 genome editing, single-cell transcriptomics, and high-throughput functional screening have broadened the scope of functional studies[9,176,182].

Clinical and biomarker data: Finally, the clues towards pathogenicity are often garnered from studying the proband and their family members in detail and scrutinizing relevant biomarkers. Analysis of the presence or absence of the variant in affected and unaffected individuals within the family, observing patterns of inheritance, and assessing whether the variant co-segregates with the disease phenotype across generations provides crucial information. Conclusive proof often involves observing the co-segregation of the variant from a different kindred[182,186].

Ethical considerations of genetic testing

The availability of genetic testing raises vital ethical issues. Informed consent is mandatory to make the individual and family members understand the implications of testing, including the potential for discovering VUS. Privacy and confidentiality are significant issues, given the sensitivity of genetic information. Additionally, the familial implications of test results can create additional dilemmas. There is a risk of discrimination based on genetic information, underscoring the need for legal protection[187]. Lastly, the psychological impact of receiving test results can be a challenge and might necessitate counselling and support. These ethical considerations highlight the need for a coordinated approach in implementing genetic testing to prioritize the rights and well-being of the care-seeker[188].

Genetic testing in resource-limited settings

Access to genetic testing may be restricted in resource-limited settings as inadequate infrastructure, lack of trained personnel, and financial constraints can be critical barriers. Shortage of genetic counsellors can be an additional constraint. The geographic variation in genetic and clinical spectrum of monogenic diabetes can further complicate management. Increasing the awareness among healthcare providers about genetic testing is important. The available resources should be optimally used based on algorithms that consider clinical information and logistic boundaries. Finally, policy changes should be instituted, promoting funding in low-resource settings for advocating cost-effective methods[187].

UNCERTAINTIES AND FUTURE RESEARCH AREAS

Many cases of monogenic diabetes remain undiagnosed due to limited awareness among healthcare providers, clinical heterogeneity, overlapping with more common types of diabetes, limited access to genetic testing, cost barriers, complex interpretation of genetic results, and low clinical suspicion in asymptomatic or mildly symptomatic cases[7]. Screening tools must be developed and validated across various ethnicities to identify candidates for genetic testing in youth-onset

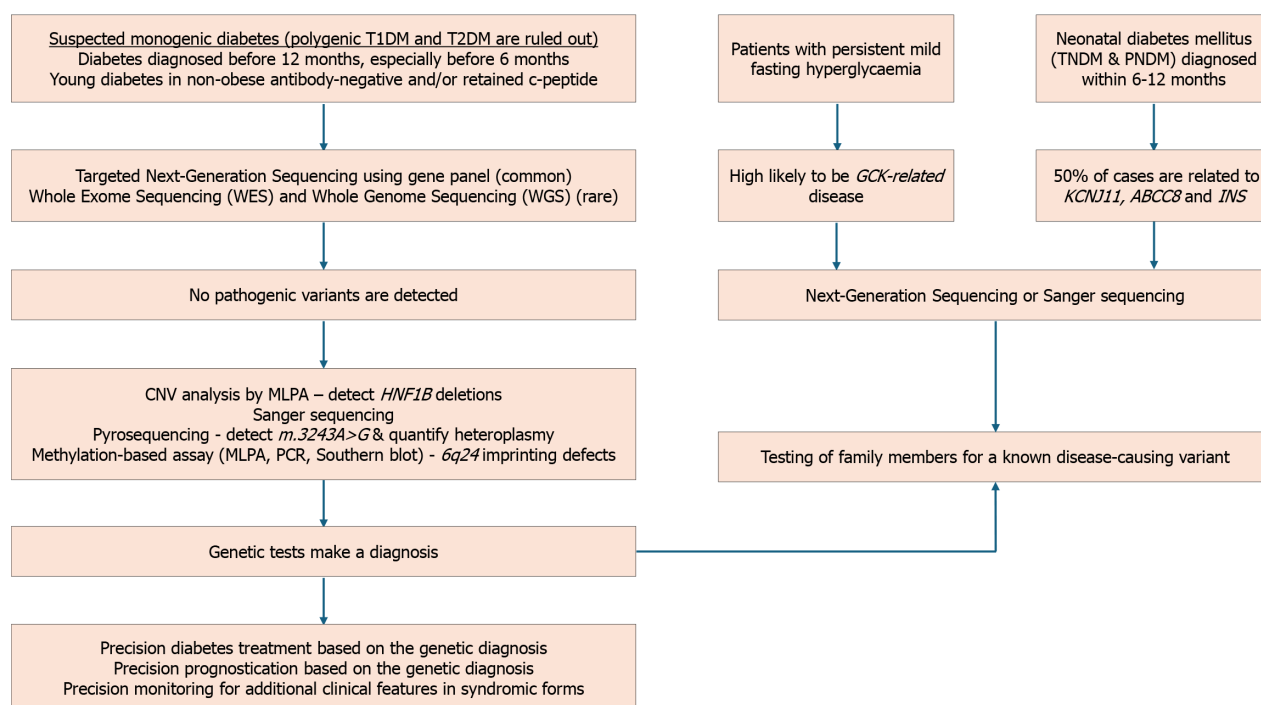


Figure 6 Best practice methods for identifying candidates for genetic screening in the diagnosis of common forms of monogenic diabetes. T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TNDM: Transient neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; CNV: Copy number variation; PCR: Polymerase chain reaction; MLPA: Multiplex ligation-dependent probe amplification.

diabetes, as population-based genetic testing is impractical.

NGS has made genetic testing accessible, but handling the data generated from extensive testing and the interpretation of the results remains an evolving process. The causal associations of many variants are generally accurate, yet false assignments are not uncommon and can have significant consequences for patients and resources[189]. Though the cost of genetic testing has come down, significant barriers persist, such as insurance coverage and diagnostic inertia, stemming from complex procedures for ordering genetic tests.

The process of evaluating evidence for variant implication involves two key steps. Firstly, the overall evidence for the involvement of a gene is assessed, primarily focusing on statistical support from genetic analyses and possibly augmented by data from informatics and functional studies. Secondly, a comprehensive evaluation of the genetic, experimental, and informatics-based support for individual candidate variants is conducted[183]. Despite advances in functional studies, the precise molecular mechanisms underlying many monogenic diabetes variants are not fully elucidated. Further research is needed to understand these mechanisms and develop targeted therapies.

The variability in disease penetrance and phenotypic expression of pathogenic variants can complicate management. While some individuals may remain asymptomatic, others may experience severe clinical symptoms, making it challenging to predict the disease course and determine appropriate interventions. Understanding the phenotypic spectrum of variants in dominant genes, from benign to disease-causing, is essential. For example, common variants in genes like *KCNJ11* and *GCK* can cause minor changes in glucose regulation, while less frequent variants with a more pronounced functional impact are associated with MODY and neonatal diabetes[39,190].

Monogenic diabetes models have advanced our understanding of diabetes pathophysiology and the genetics of common diabetes. Insights from these studies also help to interpret genome-wide association study data for T1DM and T2DM. The targets of major anti-diabetic drugs like sulfonylurea and thiazolidinedione are linked to two genes involved in the pathogenesis of monogenic diabetes, *KCNJ11* and the peroxisome proliferator-activated receptor γ , respectively.

Translating knowledge from monogenic diabetes research into effective treatments remains challenging, with direct drug development remaining elusive. However, iPSCs from monogenic diabetes represent a significant breakthrough. Differentiating iPSCs into β -like cells allows researchers to study disease mechanisms like impaired insulin secretion in a controlled laboratory setting[191]. This understanding can pave the way for newer treatments in the broader context of diabetes management[192]. The various ways in which monogenic diabetes is misdiagnosed, and its impact are given in Table 3[7,74,118,193,194].

CONCLUSION

Monogenic diabetes encompasses a diverse range of conditions stemming from single-gene defects. The condition is often misdiagnosed and mismanaged. Diagnosing monogenic diabetes is hindered by limited awareness among healthcare providers, clinical and genetic complexities, and cost barriers to genetic testing. MODY, the common form of monogenic

Table 3 Conditions that can be mistaken for monogenic diabetes, the impact of misdiagnosis, and the clinical clues for suspecting appropriate diagnosis

	Stage of life	Misdiagnosis	Clinical clues	Impact of accurate diagnosis on the management plans
<i>HNF1A</i> and <i>HNF4A</i> related diabetes	Neonate and infancy	Congenital hyperinsulinism	Transient neonatal hypoglycaemia (diazoxide discontinued in the first decade in the majority). Progresses to hyperglycemia (usually < 25 years); Association with Fanconi syndrome; Family history of diabetes; Macrosomia independent of glycaemic control (<i>HNF4A</i> -MODY is a more likely cause than <i>HNF1A</i> -MODY)	Treatment with diazoxide; Natural history differs from other causes of congenital hyperinsulinism
	Childhood and adolescence	T1DM	Islet antibodies absent within 3-5 years of diagnosis Diabetic ketoacidosis is usually absent even when omitting insulin; serum C-peptide > 0.6 ng/mL (> 0.2 nmol/L) after 3-5 years of onset; low insulin requirement (< 0.5 U/kg/day)	Stop insulin; Treat with low-dose sulfonylurea (respond initially); use other antidiabetics as necessary; avoid SGLT2i in <i>HNF1A</i> -MODY
	Adults	T2DM	Absence of features of insulin resistance; BMI in the normal range	Treat with low dose SU (respond initially); use other antidiabetics as necessary; avoid SGLT2i in <i>HNF1A</i> -MODY; Aim to reduce CVD risk despite normal lipids in <i>HNF1A</i> -MODY
	Pregnancy	GDM	Insulin is recommended therapy, consider additional glyburide if control inadequate, especially in 1 st trimester	Treat with insulin, fetal growth surveillance from 26 weeks
GCK related diabetes	Childhood and adolescence	T1DM	Stable nonprogressive mild fasting hyperglycemia; islet antibodies absent within 3-5 years of diagnosis; diabetic ketoacidosis absent on omitting insulin; strong family history	Stop insulin; pharmacological intervention is not needed
	Adults	T2DM	Stable nonprogressive mild fasting hyperglycemia; no features of insulin resistance or obesity; strong family history	Pharmacological intervention is not needed; screening for microvascular and macrovascular complications is not indicated
	Pregnancy	GDM	Stable nonprogressive mild fasting hyperglycemia; Minimal rise in plasma glucose levels after oral glucose or food	Insulin if the fetus does not have the mutation; no treatment if the fetus carries the mutation
Neonatal diabetes mellitus	Neonate and infancy	T1DM	Negative autoantibody testing; Extra-pancreatic features (gastrointestinal anomalies, congenital defects, and neurological disorders); unusual family history; small for gestational age	Should be transitioned to high-dose sulfonylurea from insulin
Mitochondrial diabetes	Adults	T2DM	Maternal inheritance; associated sensorineural hearing loss or progressive external ophthalmoplegia at an early age	Oral antidiabetics; may require insulin later; avoid metformin

MODY: Maturity-onset diabetes of the young; SU: Sulfonylurea; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; SGLT2i: Sodium-glucose co-transporter-2 inhibitor; GDM: Gestational diabetes mellitus; CVD: Cardiovascular disease.

diabetes, is suspected based on early-onset diabetes, family history, and biomarkers, with confirmation usually through NGS. NDM, affecting infants typically before 6 months of age, necessitates early genetic testing for accurate diagnosis and tailored management. Management of monogenic diabetes opens the window for precision medicine, largely made possible by broader availability and accessibility of NGS. Targeted gene panels offer specificity and cost-effectiveness, although WES offers wider opportunities for gene discovery. NGS has increased the accessibility of genetic testing but also has led to the identification of VUS. Advanced computational models, functional studies, and segregation analysis for pathogenicity assessment are required to understand the significance of VUS. Increased awareness, accessibility to genetic testing, and continued research are pivotal for overcoming challenges and providing precision care in monogenic diabetes mellitus.

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REFERENCES

- 1 Shepherd M, Shields B, Hammersley S, Hudson M, McDonald TJ, Colclough K, Oram RA, Knight B, Hyde C, Cox J, Mallam K, Moudiotis C, Smith R, Fraser B, Robertson S, Greene S, Ellard S, Pearson ER, Hattersley AT; UNITED Team. Systematic Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. *Diabetes Care* 2016; **39**: 1879-1888 [PMID: 27271189 DOI: 10.2337/dc16-0645]
- 2 Bansal V, Gassenhuber J, Phillips T, Oliveira G, Harbaugh R, Villarasa N, Topol EJ, Seufferlein T, Boehm BO. Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6888 individuals. *BMC Med* 2017; **15**: 213 [PMID: 29207974 DOI: 10.1186/s12916-017-0977-3]
- 3 IDF Diabetes Atlas. IDF Diabetes Atlas Reports. [cited March 04, 2025]. Available from: <https://diabetesatlas.org/atlas-reports/>
- 4 Bonnefond A, Unnikrishnan R, Doria A, Vaxillaire M, Kulkarni RN, Mohan V, Trischitta V, Froguel P. Monogenic diabetes. *Nat Rev Dis Primers* 2023; **9**: 12 [PMID: 36894549 DOI: 10.1038/s41572-023-00421-w]
- 5 Greeley SAW, Polak M, Njolstad PR, Barbetti F, Williams R, Castano L, Raile K, Chi DV, Habeb A, Hattersley AT, Codner E. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2022; **23**: 1188-1211 [PMID: 36537518 DOI: 10.1111/pedi.13426]
- 6 Owen KR. Monogenic diabetes: old and new approaches to diagnosis. *Clin Med (Lond)* 2013; **13**: 278-281 [PMID: 23760703 DOI: 10.7861/clinmedicine.13-3-278]
- 7 Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia* 2010; **53**: 2504-2508 [PMID: 20499044 DOI: 10.1007/s00125-010-1799-4]
- 8 Yeung RO, Hannah-Shmouni F, Niederhoffer K, Walker MA. Not quite type 1 or type 2, what now? Review of monogenic, mitochondrial, and syndromic diabetes. *Rev Endocr Metab Disord* 2018; **19**: 35-52 [PMID: 29777474 DOI: 10.1007/s11154-018-9446-3]
- 9 Murphy R, Colclough K, Pollin TI, Ikle JM, Svalastoga P, Maloney KA, Saint-Martin C, Molnes J, ADA/EASD PMDI, Misra S, Aukrust I, de Franco E, Flanagan SE, Njolstad PR, Billings LK, Owen KR, Gloyn AL. The use of precision diagnostics for monogenic diabetes: a systematic review and expert opinion. *Commun Med (Lond)* 2023; **3**: 136 [PMID: 37794142 DOI: 10.1038/s43856-023-00369-8]
- 10 Harris AG, Letourneau LR, Greeley SAW. Monogenic diabetes: the impact of making the right diagnosis. *Curr Opin Pediatr* 2018; **30**: 558-567 [PMID: 29846255 DOI: 10.1097/MOP.0000000000000643]
- 11 Campbell MR. Review of current status of molecular diagnosis and characterization of monogenic diabetes mellitus: a focus on next-generation sequencing. *Expert Rev Mol Diagn* 2020; **20**: 413-420 [PMID: 32050823 DOI: 10.1080/14737159.2020.1730179]
- 12 Vaxillaire M, Froguel P, Bonnefond A. How Recent Advances in Genomics Improve Precision Diagnosis and Personalized Care of Maturity-Onset Diabetes of the Young. *Curr Diab Rep* 2019; **19**: 79 [PMID: 31385057 DOI: 10.1007/s11892-019-1202-x]
- 13 Zammouri J, Vatie C, Capel E, Auclair M, Storey-London C, Bismuth E, Mosbah H, Donadille B, Janmaat S, Fève B, Jéru I, Vigouroux C. Molecular and Cellular Bases of Lipodystrophy Syndromes. *Front Endocrinol (Lausanne)* 2021; **12**: 803189 [PMID: 35046902 DOI: 10.3389/fendo.2021.803189]
- 14 Iqbal J, Jiang HL, Wu HX, Li L, Zhou YH, Hu N, Xiao F, Wang T, Xu SN, Zhou HD. Hereditary severe insulin resistance syndrome: Pathogenesis, pathophysiology, and clinical management. *Genes Dis* 2023; **10**: 1846-1856 [PMID: 37492723 DOI: 10.1016/j.gendis.2022.03.016]
- 15 Balasubramanyam A. Defining and Classifying New Subgroups of Diabetes. *Annu Rev Med* 2021; **72**: 63-74 [PMID: 33064971 DOI: 10.1146/annurev-med-050219-034524]
- 16 Antal Z. Maturity-Onset Diabetes of the Young (MODY): Genetic Causes, Clinical Characteristics, Considerations for Testing, and Treatment Options. *Endocrines* 2021; **2**: 485-501 [DOI: 10.3390/endocrines2040043]
- 17 Polak M, Cavé H. Neonatal diabetes mellitus: a disease linked to multiple mechanisms. *Orphanet J Rare Dis* 2007; **2**: 12 [PMID: 17349054 DOI: 10.1186/1750-1172-2-12]
- 18 Beltrand J, Busiah K, Vaivre-Douret L, Fauret AL, Berdugo M, Cavé H, Polak M. Neonatal Diabetes Mellitus. *Front Pediatr* 2020; **8**: 540718

- [PMID: 33102403 DOI: 10.3389/fped.2020.540718]
- 19 **Nkonge KM**, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). *Clin Diabetes Endocrinol* 2020; **6**: 20 [PMID: 33292863 DOI: 10.1186/s40842-020-00112-5]
 - 20 **Yahaya TO**, Ufuoma SB. Genetics and Pathophysiology of Maturity-onset Diabetes of the Young (MODY): A Review of Current Trends. *Oman Med J* 2020; **35**: e126 [PMID: 32489678 DOI: 10.5001/omj.2020.44]
 - 21 **Yee ML**, Wong R, Datta M, Fazlo TN, Ebrahim MM, Mcnamara EC, De Jong G, Gilfillan C. Mitochondrial disease: an uncommon but important cause of diabetes mellitus. *Endocrinol Diabetes Metab Case Rep* 2018; **2018** [PMID: 30306776 DOI: 10.1530/EDM-18-0091]
 - 22 **Urano F**. Wolfram Syndrome: Diagnosis, Management, and Treatment. *Curr Diab Rep* 2016; **16**: 6 [PMID: 26742931 DOI: 10.1007/s11892-015-0702-6]
 - 23 **Lu H**, Lu H, Vaucher J, Tran C, Vollenweider P, Castioni J. [Thiamine-responsive megaloblastic anemia or Rogers syndrome: A literature review]. *Rev Med Interne* 2019; **40**: 20-27 [PMID: 30031565 DOI: 10.1016/j.revmed.2018.06.005]
 - 24 **Senniappan S**, Hughes M, Shah P, Shah V, Kaski JP, Brogan P, Hussain K. Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) syndrome is associated with severe chronic inflammation and cardiomyopathy, and represents a new monogenic autoinflammatory syndrome. *J Pediatr Endocrinol Metab* 2013; **26**: 877-882 [PMID: 23729543 DOI: 10.1515/jpem-2013-0062]
 - 25 **Lighthourne M**, Brown RJ. Genetics of Lipodystrophy. *Endocrinol Metab Clin North Am* 2017; **46**: 539-554 [PMID: 28476236 DOI: 10.1016/j.ecl.2017.01.012]
 - 26 **Patni N**, Garg A. Lipodystrophy for the Diabetologist-What to Look For. *Curr Diab Rep* 2022; **22**: 461-470 [PMID: 35821558 DOI: 10.1007/s11892-022-01485-w]
 - 27 **Semple RK**, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genetic syndromes of severe insulin resistance. *Endocr Rev* 2011; **32**: 498-514 [PMID: 21536711 DOI: 10.1210/er.2010-0020]
 - 28 **Perge K**, Capel E, Villanueva C, Gautheron J, Diallo S, Auclair M, Rondeau S, Morichon R, Brioude F, Jéru I, Rossi M, Nicolino M, Vigouroux C. Ciliopathy due to POC1A deficiency: clinical and metabolic features, and cellular modeling. *Eur J Endocrinol* 2024; **190**: 151-164 [PMID: 38245004 DOI: 10.1093/ajendo/lvae009]
 - 29 **Bennett CL**, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 2001; **27**: 20-21 [PMID: 11137993 DOI: 10.1038/83713]
 - 30 **Ben-Skowronek I**. IPEX Syndrome: Genetics and Treatment Options. *Genes (Basel)* 2021; **12**: 323 [PMID: 33668198 DOI: 10.3390/genes12030323]
 - 31 **Verbsky JW**, Chatila TA. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. *Curr Opin Pediatr* 2013; **25**: 708-714 [PMID: 24240290 DOI: 10.1097/MOP.0000000000000029]
 - 32 **Sacks DB**, Arnold M, Bakris GL, Bruns DE, Horvath AR, Lernmark Å, Metzger BE, Nathan DM, Kirkman MS. Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus. *Clin Chem* 2023; **69**: 808-868 [PMID: 37473453 DOI: 10.1093/clinchem/hvad080]
 - 33 **Riddle MC**, Philipson LH, Rich SS, Carlsson A, Franks PW, Greeley SAW, Nolan JJ, Pearson ER, Zeitler PS, Hattersley AT. Monogenic Diabetes: From Genetic Insights to Population-Based Precision in Care. Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care* 2020; **43**: 3117-3128 [PMID: 33560999 DOI: 10.2337/dci20-0065]
 - 34 **Hattersley AT**. Laboratory Guidelines Are Needed for Diagnostic Genetic Testing for Monogenic Diabetes. *Clin Chem* 2023; **69**: 788-790 [PMID: 37473454 DOI: 10.1093/clinchem/hvad093]
 - 35 **Shimada A**, Kawasaki E, Abiru N, Awata T, Oikawa Y, Osawa H, Kajio H, Kozawa J, Takahashi K, Chujo D, Noso S, Fukui T, Miura J, Yasuda K, Yasuda H, Imagawa A, Ikegami H. New diagnostic criteria (2023) for slowly progressive type 1 diabetes (SPIDDM): Report from Committee on Type 1 Diabetes of the Japan Diabetes Society (English version). *J Diabetes Investig* 2024; **15**: 254-257 [PMID: 38184802 DOI: 10.1111/jdi.14121]
 - 36 **Murphy R**, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. *Nat Clin Pract Endocrinol Metab* 2008; **4**: 200-213 [PMID: 18301398 DOI: 10.1038/ncpendmet0778]
 - 37 **Valkovicova T**, Skopkova M, Stanik J, Gasperikova D. Novel insights into genetics and clinics of the HNF1A-MODY. *Endocr Regul* 2019; **53**: 110-134 [PMID: 31517624 DOI: 10.2478/enr-2019-0013]
 - 38 **Gardner DS**, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). *Diabetes Metab Syndr Obes* 2012; **5**: 101-108 [PMID: 22654519 DOI: 10.2147/DMSO.S23353]
 - 39 **Hulín J**, Škopková M, Valkovičová T, Mikulajová S, Rosol'anková M, Papcun P, Gašperíková D, Staník J. Clinical implications of the glucokinase impaired function - GCK MODY today. *Physiol Res* 2020; **69**: 995-1011 [PMID: 33129248 DOI: 10.33549/physiolres.934487]
 - 40 **Shih DQ**, Dansky HM, Fleisher M, Assmann G, Fajans SS, Stoffel M. Genotype/phenotype relationships in HNF-4alpha/MODY1: haploinsufficiency is associated with reduced apolipoprotein (AII), apolipoprotein (CIII), lipoprotein(a), and triglyceride levels. *Diabetes* 2000; **49**: 832-837 [PMID: 10905494 DOI: 10.2337/diabetes.49.5.832]
 - 41 **Gambella A**, Kalantari S, Cadamuro M, Quaglia M, Delvecchio M, Fabris L, Pinon M. The Landscape of HNF1B Deficiency: A Syndrome Not Yet Fully Explored. *Cells* 2023; **12**: 307 [PMID: 36672242 DOI: 10.3390/cells12020307]
 - 42 **Warncke K**, Kummer S, Raile K, Grulich-Henn J, Woelfle J, Steichen E, Prinz N, Holl RW. Frequency and Characteristics of MODY 1 (HNF4A Mutation) and MODY 5 (HNF1B Mutation): Analysis From the DPV Database. *J Clin Endocrinol Metab* 2019; **104**: 845-855 [PMID: 30535056 DOI: 10.1210/je.2018-01696]
 - 43 **Abreu GM Miss**, Tarantino RM, da Fonseca ACP, de Souza RB, Soares CAPD, Cabello PH, Rodacki M, Zajdenverg L, Zembrzusi VM, Campos Junior M. PDX1-MODY: A rare missense mutation as a cause of monogenic diabetes. *Eur J Med Genet* 2021; **64**: 104194 [PMID: 33746035 DOI: 10.1016/j.ejmg.2021.104194]
 - 44 **Horikawa Y**, Enya M. Genetic Dissection and Clinical Features of MODY6 (NEUROD1-MODY). *Curr Diab Rep* 2019; **19**: 12 [PMID: 30793219 DOI: 10.1007/s11892-019-1130-9]
 - 45 **Laver TW**, Wakeling MN, Knox O, Colclough K, Wright CF, Ellard S, Hattersley AT, Weedon MN, Patel KA. Evaluation of Evidence for Pathogenicity Demonstrates That BLK, KLF11, and PAX4 Should Not Be Included in Diagnostic Testing for MODY. *Diabetes* 2022; **71**: 1128-1136 [PMID: 35108381 DOI: 10.2337/db21-0844]
 - 46 **Sun S**, Gong S, Li M, Wang X, Wang F, Cai X, Liu W, Luo Y, Zhang S, Zhang R, Zhou L, Zhu Y, Ma Y, Ren Q, Zhang X, Chen J, Chen L, Wu J, Gao L, Zhou X, Li Y, Zhong L, Han X, Ji L. Clinical and genetic characteristics of CEL-MODY (MODY8): a literature review and screening in Chinese individuals diagnosed with early-onset type 2 diabetes. *Endocrine* 2024; **83**: 99-109 [PMID: 37726640 DOI: 10.1007/s12005-024-01000-0]

- 10.1007/s12020-023-03512-6]
- 47 **Ovsyannikova AK**, Rymar OD, Shakhtshneider EV, Klimontov VV, Koroleva EA, Myakina NE, Voevoda MI. ABCC8-Related Maturity-Onset Diabetes of the Young (MODY12): Clinical Features and Treatment Perspective. *Diabetes Ther* 2016; **7**: 591-600 [PMID: [27538677](#) DOI: [10.1007/s13300-016-0192-9](#)]
 - 48 **Bonnefond A**, Philippe J, Durand E, Dechaume A, Huyvaert M, Montagne L, Marre M, Balkau B, Fajardy I, Vambergue A, Vatin V, Delplanque J, Le Guilcher D, De Graeve F, Lecoœur C, Sand O, Vaxillaire M, Froguel P. Whole-exome sequencing and high throughput genotyping identified KCNJ11 as the thirteenth MODY gene. *PLoS One* 2012; **7**: e37423 [PMID: [22701567](#) DOI: [10.1371/journal.pone.0037423](#)]
 - 49 **Ivanoshchuk DE**, Shakhtshneider EV, Rymar OD, Ovsyannikova AK, Mikhailova SV, Orlov PS, Ragino YI, Voevoda MI. Analysis of APPL1 Gene Polymorphisms in Patients with a Phenotype of Maturity Onset Diabetes of the Young. *J Pers Med* 2020; **10**: 100 [PMID: [32854233](#) DOI: [10.3390/jpm10030100](#)]
 - 50 **Şimşek E**, Çilingir O, Şimşek T, Kocagil S, Erzurumluoğlu Gökalep E, Demiral M, Binay C. Screening of Mutations in Maturity-onset Diabetes of the Young-related Genes and RFX6 in Children with Autoantibody-negative Type 1 Diabetes Mellitus. *J Clin Res Pediatr Endocrinol* 2024; **16**: 137-145 [PMID: [38054414](#) DOI: [10.4274/jcrpe.galenos.2023.2023-5-10](#)]
 - 51 **Shield JP**, Gardner RJ, Wadsworth EJ, Whiteford ML, James RS, Robinson DO, Baum JD, Temple IK. Aetiopathology and genetic basis of neonatal diabetes. *Arch Dis Child Fetal Neonatal Ed* 1997; **76**: F39-F42 [PMID: [9059185](#) DOI: [10.1136/fn.76.1.f39](#)]
 - 52 **Kocova M**. Genetic Spectrum of Neonatal Diabetes. *Balkan J Med Genet* 2020; **23**: 5-15 [PMID: [33816067](#) DOI: [10.2478/bjmg-2020-0027](#)]
 - 53 **Shimomura K**, Maejima Y. K(ATP) Channel Mutations and Neonatal Diabetes. *Intern Med* 2017; **56**: 2387-2393 [PMID: [28824061](#) DOI: [10.2169/internalmedicine.8454-16](#)]
 - 54 **Støy J**, Edgill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, Below JE, Hayes MG, Cox NJ, Lipkind GM, Lipton RB, Greeley SA, Patch AM, Ellard S, Steiner DF, Hattersley AT, Philipson LH, Bell GI; Neonatal Diabetes International Collaborative Group. Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc Natl Acad Sci U S A* 2007; **104**: 15040-15044 [PMID: [17855560](#) DOI: [10.1073/pnas.0707291104](#)]
 - 55 **Mackay DJ**, Temple IK. Transient neonatal diabetes mellitus type 1. *Am J Med Genet C Semin Med Genet* 2010; **154C**: 335-342 [PMID: [20803656](#) DOI: [10.1002/ajmg.c.30272](#)]
 - 56 **Julier C**, Nicolino M. Wolcott-Rallison syndrome. *Orphanet J Rare Dis* 2010; **5**: 29 [PMID: [21050479](#) DOI: [10.1186/1750-1172-5-29](#)]
 - 57 **Shaw-Smith C**, De Franco E, Lango Allen H, Battle M, Flanagan SE, Borowiec M, Taplin CE, van Alfen-van der Velden J, Cruz-Rojó J, Perez de Nanclares G, Miedzybrodzka Z, Deja G, Wlodarska I, Mlynarski W, Ferrer J, Hattersley AT, Ellard S. GATA4 mutations are a cause of neonatal and childhood-onset diabetes. *Diabetes* 2014; **63**: 2888-2894 [PMID: [24696446](#) DOI: [10.2337/db14-0061](#)]
 - 58 **Yue X**, Luo Y, Wang J, Huang D. Monogenic Diabetes with GATA6 Mutations: Characterization of a Novel Family and a Comprehensive Analysis of the GATA6 Clinical and Genetics Traits. *Mol Biotechnol* 2024; **66**: 467-474 [PMID: [37204622](#) DOI: [10.1007/s12033-023-00761-8](#)]
 - 59 **Passone CGB**, Vermillac G, Staels W, Besancon A, Kariyawasam D, Godot C, Lambe C, Talbotec C, Girard M, Chardot C, Berteloot L, Hachem T, Lapillonne A, Poidvin A, Storey C, Neve M, Stan C, Dugelay E, Fauret-Amsellem AL, Capri Y, Cavé H, Ybarra M, Chandra V, Scharfmann R, Bismuth E, Polak M, Carel JC, Pigneur B, Beltrand J. Mitchell-Riley Syndrome: Improving Clinical Outcomes and Searching for Functional Impact of RFX-6 Mutations. *Front Endocrinol (Lausanne)* 2022; **13**: 802351 [PMID: [35813646](#) DOI: [10.3389/fendo.2022.802351](#)]
 - 60 **London S**, De Franco E, Elias-Assad G, Barhoum MN, Felszer C, Paniakov M, Weiner SA, Tenenbaum-Rakover Y. Case Report: Neonatal Diabetes Mellitus Caused by a Novel GLIS3 Mutation in Twins. *Front Endocrinol (Lausanne)* 2021; **12**: 673755 [PMID: [34093443](#) DOI: [10.3389/fendo.2021.673755](#)]
 - 61 **Wen X**, Yang Y. Emerging roles of GLIS3 in neonatal diabetes, type 1 and type 2 diabetes. *J Mol Endocrinol* 2017; **58**: R73-R85 [PMID: [27899417](#) DOI: [10.1530/JME-16-0232](#)]
 - 62 **Demirbilek H**, Cayir A, Flanagan SE, Yıldırım R, Kor Y, Gurbuz F, Haliloğlu B, Yıldız M, Baran RT, Akbas ED, Demiral M, Ünal E, Arslan G, Vuralı D, Buyukyilmaz G, Al-Khawaga S, Saeed A, Al Maadheed M, Khalifa A, Onal H, Yuksel B, Ozbek MN, Bereket A, Hattersley AT, Hussain K, De Franco E. Clinical Characteristics and Long-term Follow-up of Patients with Diabetes Due To PTF1A Enhancer Mutations. *J Clin Endocrinol Metab* 2020; **105**: e4351-e4359 [PMID: [32893856](#) DOI: [10.1210/clinem/dgaa613](#)]
 - 63 **Delvecchio M**, Pastore C, Giordano P. Treatment Options for MODY Patients: A Systematic Review of Literature. *Diabetes Ther* 2020; **11**: 1667-1685 [PMID: [32583173](#) DOI: [10.1007/s13300-020-00864-4](#)]
 - 64 **Lau HH**, Ng NHJ, Loo LSW, Jasmen JB, Teo AKK. The molecular functions of hepatocyte nuclear factors - In and beyond the liver. *J Hepatol* 2018; **68**: 1033-1048 [PMID: [29175243](#) DOI: [10.1016/j.jhep.2017.11.026](#)]
 - 65 **Miyachi Y**, Miyazawa T, Ogawa Y. HNF1A Mutations and Beta Cell Dysfunction in Diabetes. *Int J Mol Sci* 2022; **23** [PMID: [35328643](#) DOI: [10.3390/ijms23063222](#)]
 - 66 **Torsvik J**, Johansson S, Johansen A, Ek J, Minton J, Raeder H, Ellard S, Hattersley A, Pedersen O, Hansen T, Molven A, Njølstad PR. Mutations in the VNTR of the carboxyl-ester lipase gene (CEL) are a rare cause of monogenic diabetes. *Hum Genet* 2010; **127**: 55-64 [PMID: [19760265](#) DOI: [10.1007/s00439-009-0740-8](#)]
 - 67 **Molven A**, Ringdal M, Nordbø AM, Raeder H, Støy J, Lipkind GM, Steiner DF, Philipson LH, Bergmann I, Aarskog D, Undlien DE, Joner G, Søvik O; Norwegian Childhood Diabetes Study Group, Bell GI, Njølstad PR. Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. *Diabetes* 2008; **57**: 1131-1135 [PMID: [18192540](#) DOI: [10.2337/db07-1467](#)]
 - 68 **De Franco E**, Saint-Martin C, Brusgaard K, Knight Johnson AE, Aguilar-Bryan L, Bowman P, Arnoux JB, Larsen AR, Sanyoura M, Greeley SAW, Calzada-León R, Harman B, Houghton JAL, Nishimura-Meguro E, Laver TW, Ellard S, Del Gaudio D, Christesen HT, Bellanné-Chantelot C, Flanagan SE. Update of variants identified in the pancreatic β -cell K(ATP) channel genes KCNJ11 and ABCC8 in individuals with congenital hyperinsulinism and diabetes. *Hum Mutat* 2020; **41**: 884-905 [PMID: [32027066](#) DOI: [10.1002/humu.23995](#)]
 - 69 **Cheng KK**, Lam KS, Wu D, Wang Y, Sweeney G, Hoo RL, Zhang J, Xu A. APPL1 potentiates insulin secretion in pancreatic β cells by enhancing protein kinase Akt-dependent expression of SNARE proteins in mice. *Proc Natl Acad Sci U S A* 2012; **109**: 8919-8924 [PMID: [22566644](#) DOI: [10.1073/pnas.1202435109](#)]
 - 70 **Carmody D**, Naylor RN, Bell CD, Berry S, Montgomery JT, Tadie EC, Hwang JL, Greeley SA, Philipson LH. GCK-MODY in the US National Monogenic Diabetes Registry: frequently misdiagnosed and unnecessarily treated. *Acta Diabetol* 2016; **53**: 703-708 [PMID: [27106716](#) DOI: [10.1007/s00592-016-0859-8](#)]
 - 71 **Bellanné-Chantelot C**, Carette C, Riveline JP, Valéro R, Gautier JF, Larger E, Reznik Y, Ducluzeau PH, Sola A, Hartemann-Heurtier A,

- Lecomte P, Chaillous L, Laloi-Michelin M, Wilhem JM, Cuny P, Duron F, Guerci B, Jeandidier N, Mosnier-Pudar H, Assayag M, Dubois-Laforgue D, Velho G, Timsit J. The type and the position of HNF1A mutation modulate age at diagnosis of diabetes in patients with maturity-onset diabetes of the young (MODY)-3. *Diabetes* 2008; **57**: 503-508 [PMID: 18003757 DOI: 10.2337/db07-0859]
- 72 **Broome DT**, Pantalone KM, Kashyap SR, Philipson LH. Approach to the Patient with MODY-Monogenic Diabetes. *J Clin Endocrinol Metab* 2021; **106**: 237-250 [PMID: 33034350 DOI: 10.1210/clinem/dgaa710]
- 73 **Kleinberger JW**, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, Shuldiner AR, Tollefsen S, White NH, Pollin TI. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. *Genet Med* 2018; **20**: 583-590 [PMID: 29758564 DOI: 10.1038/gim.2017.150]
- 74 **Urakami T**. Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. *Diabetes Metab Syndr Obes* 2019; **12**: 1047-1056 [PMID: 31360071 DOI: 10.2147/DMSO.S179793]
- 75 **Colclough K**, Bellanne-Chantelot C, Saint-Martin C, Flanagan SE, Ellard S. Mutations in the genes encoding the transcription factors hepatocyte nuclear factor 1 alpha and 4 alpha in maturity-onset diabetes of the young and hyperinsulinemic hypoglycemia. *Hum Mutat* 2013; **34**: 669-685 [PMID: 23348805 DOI: 10.1002/humu.22279]
- 76 **Cromer SJ**, Sella AC, Rosenberg E, Scully K, McDonnell M, Abreu AP, Weil M, Bernstein SN, Quinn M, Powe C, Mitchell DM, Udler MS. Report of Prolonged Neonatal Hypoglycemia in Three Infants of Mothers With Variants in HNF1A. *AACE Clin Case Rep* 2022; **8**: 224-230 [PMID: 36189138 DOI: 10.1016/j.aace.2022.07.004]
- 77 **Owen KR**, Thanabalasingham G, James TJ, Karpe F, Farmer AJ, McCarthy MI, Gloyn AL. Assessment of high-sensitivity C-reactive protein levels as diagnostic discriminator of maturity-onset diabetes of the young due to HNF1A mutations. *Diabetes Care* 2010; **33**: 1919-1924 [PMID: 20724646 DOI: 10.2337/dc10-0288]
- 78 **McDonald TJ**, Shields BM, Lawry J, Owen KR, Gloyn AL, Ellard S, Hattersley AT. High-sensitivity CRP discriminates HNF1A-MODY from other subtypes of diabetes. *Diabetes Care* 2011; **34**: 1860-1862 [PMID: 21700917 DOI: 10.2337/dc11-0323]
- 79 **Toniatti C**, Demartis A, Monaci P, Nicosia A, Ciliberto G. Synergistic trans-activation of the human C-reactive protein promoter by transcription factor HNF-1 binding at two distinct sites. *EMBO J* 1990; **9**: 4467-4475 [PMID: 2265613 DOI: 10.1002/j.1460-2075.1990.tb07897.x]
- 80 **Szopa M**, Klupa T, Kapusta M, Matejko B, Ucieklak D, Glodzik W, Zapala B, Sani CM, Hohendorf J, Malecki MT, Skupien J. A decision algorithm to identify patients with high probability of monogenic diabetes due to HNF1A mutations. *Endocrine* 2019; **64**: 75-81 [PMID: 30778899 DOI: 10.1007/s12020-019-01863-7]
- 81 **Bellanné-Chantelot C**, Coste J, Ciangura C, Fonfrère M, Saint-Martin C, Bouché C, Sonnet E, Valéro R, Lévy DJ, Dubois-Laforgue D, Timsit J; Monogenic Diabetes Study Group of the Société Francophone du Diabète (SFD). High-sensitivity C-reactive protein does not improve the differential diagnosis of HNF1A-MODY and familial young-onset type 2 diabetes: A grey zone analysis. *Diabetes Metab* 2016; **42**: 33-37 [PMID: 25753245 DOI: 10.1016/j.diabet.2015.02.001]
- 82 **Juszczak A**, Pavić T, Vučković F, Bennett AJ, Shah N, Pape Medvidović E, Groves CJ, Šekerija M, Chandler K, Burrows C, Rojnić Putarek N, Vučić Lovrenčić M, Čuća Knežević J, James TJ, Gloyn AL, Lauc G, McCarthy MI, Owen KR, Gornik O. Plasma Fucosylated Glycans and C-Reactive Protein as Biomarkers of HNF1A-MODY in Young Adult-Onset Nonautoimmune Diabetes. *Diabetes Care* 2019; **42**: 17-26 [PMID: 30455330 DOI: 10.2337/dc18-0422]
- 83 **Thanabalasingham G**, Pal A, Selwood MP, Dudley C, Fisher K, Bingley PJ, Ellard S, Farmer AJ, McCarthy MI, Owen KR. Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. *Diabetes Care* 2012; **35**: 1206-1212 [PMID: 22432108 DOI: 10.2337/dc11-1243]
- 84 **Pontoglio M**, Prié D, Cheret C, Doyen A, Leroy C, Froguel P, Velho G, Yaniv M, Friedlander G. HNF1alpha controls renal glucose reabsorption in mouse and man. *EMBO Rep* 2000; **1**: 359-365 [PMID: 11269503 DOI: 10.1093/embo-reports/kvd071]
- 85 **Menzel R**, Kaisaki PJ, Rjasanowski I, Heinke P, Kerner W, Menzel S. A low renal threshold for glucose in diabetic patients with a mutation in the hepatocyte nuclear factor-1alpha (HNF-1alpha) gene. *Diabet Med* 1998; **15**: 816-820 [PMID: 9796880 DOI: 10.1002/(SICI)1096-9136(199810)15:10<816::AID-DIA714>3.0.CO;2-P]
- 86 **Bingham C**, Ellard S, Nicholls AJ, Pennock CA, Allen J, James AJ, Satchell SC, Salzmann MB, Hattersley AT. The generalized aminoaciduria seen in patients with hepatocyte nuclear factor-1alpha mutations is a feature of all patients with diabetes and is associated with glucosuria. *Diabetes* 2001; **50**: 2047-2052 [PMID: 11522670 DOI: 10.2337/diabetes.50.9.2047]
- 87 **Stride A**, Ellard S, Clark P, Shakespeare L, Salzmann M, Shepherd M, Hattersley AT. Beta-cell dysfunction, insulin sensitivity, and glycosuria precede diabetes in hepatocyte nuclear factor-1alpha mutation carriers. *Diabetes Care* 2005; **28**: 1751-1756 [PMID: 15983330 DOI: 10.2337/diacare.28.7.1751]
- 88 **Yin L**, Ma H, Ge X, Edwards PA, Zhang Y. Hepatic hepatocyte nuclear factor 4a is essential for maintaining triglyceride and cholesterol homeostasis. *Arterioscler Thromb Vasc Biol* 2011; **31**: 328-336 [PMID: 21071704 DOI: 10.1161/ATVBAHA.110.217828]
- 89 **McDonald TJ**, McEneny J, Pearson ER, Thanabalasingham G, Szopa M, Shields BM, Ellard S, Owen KR, Malecki MT, Hattersley AT, Young IS. Lipoprotein composition in HNF1A-MODY: differentiating between HNF1A-MODY and type 2 diabetes. *Clin Chim Acta* 2012; **413**: 927-932 [PMID: 22360925 DOI: 10.1016/j.cca.2012.02.005]
- 90 **Pearson ER**, Pruhova S, Tack CJ, Johansen A, Castleden HA, Lumb PJ, Wierzbicki AS, Clark PM, Lebl J, Pedersen O, Ellard S, Hansen T, Hattersley AT. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. *Diabetologia* 2005; **48**: 878-885 [PMID: 15830177 DOI: 10.1007/s00125-005-1738-y]
- 91 **Ping F**, Fu J, Xiao X. Distinguishing the lipid profile of GCK-MODY patients and its correlation with hsCRP levels. *Front Endocrinol (Lausanne)* 2022; **13**: 1024431 [PMID: 36387841 DOI: 10.3389/fendo.2022.1024431]
- 92 **Fendler W**, Borowiec M, Antosik K, Szadkowska A, Deja G, Jarosz-Chobot P, Mysliwiec M, Wyka K, Pietrzak I, Skupien J, Malecki MT, Mlynarski W. HDL cholesterol as a diagnostic tool for clinical differentiation of GCK-MODY from HNF1A-MODY and type 1 diabetes in children and young adults. *Clin Endocrinol (Oxf)* 2011; **75**: 321-327 [PMID: 21521320 DOI: 10.1111/j.1365-2265.2011.04052.x]
- 93 **Fendler W**, Rizzo M, Borowiec M, Malachowska B, Antosik K, Szadkowska A, Banach M, Urbanska-Kosinska M, Szopa M, Malecki M, Mlynarski W. Less but better: cardioprotective lipid profile of patients with GCK-MODY despite lower HDL cholesterol level. *Acta Diabetol* 2014; **51**: 625-632 [PMID: 24549415 DOI: 10.1007/s00592-014-0567-1]
- 94 **Besser RE**, Shepherd MH, McDonald TJ, Shields BM, Knight BA, Ellard S, Hattersley AT. Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-{alpha}/hepatocyte nuclear factor 4-{alpha} maturity-onset diabetes of the young from long-duration type 1 diabetes. *Diabetes Care* 2011; **34**: 286-291 [PMID: 21270186 DOI: 10.2337/dc10-1293]
- 95 **Wang Y**, Gao Y, Cai X, Chen L, Zhou L, Ma Y, Gong S, Han X, Ji L. Clinical Implications of Urinary C-Peptide Creatinine Ratio in Patients

- with Different Types of Diabetes. *J Diabetes Res* 2019; **2019**: 1747684 [PMID: 31485449 DOI: 10.1155/2019/1747684]
- 96 Angelescu MA, Andronic O, Dima SO, Popescu I, Meivar-Levy I, Ferber S, Lixandru D. miRNAs as Biomarkers in Diabetes: Moving towards Precision Medicine. *Int J Mol Sci* 2022; **23** [PMID: 36361633 DOI: 10.3390/ijms232112843]
 - 97 Nowak N, Hohendorff J, Solecka I, Szopa M, Skupien J, Kiec-Wilk B, Mlynarski W, Malecki MT. Circulating ghrelin level is higher in HNF1A-MODY and GCK-MODY than in polygenic forms of diabetes mellitus. *Endocrine* 2015; **50**: 643-649 [PMID: 25987348 DOI: 10.1007/s12020-015-0627-5]
 - 98 Mughal SA, Park R, Nowak N, Gloyn AL, Karpe F, Matile H, Malecki MT, McCarthy MI, Stoffel M, Owen KR. Apolipoprotein M can discriminate HNF1A-MODY from Type 1 diabetes. *Diabet Med* 2013; **30**: 246-250 [PMID: 23157689 DOI: 10.1111/dme.12066]
 - 99 Firdous P, Nissar K, Masoodi SR, Ganai BA. Biomarkers: Tools for Discriminating MODY from Other Diabetic Subtypes. *Indian J Endocrinol Metab* 2022; **26**: 223-231 [PMID: 36248040 DOI: 10.4103/ijem.ijem_266_21]
 - 100 Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia* 2012; **55**: 1265-1272 [PMID: 22218698 DOI: 10.1007/s00125-011-2418-8]
 - 101 Zhao J, Chen Y, Ma F, Shu H, Zheng L, Liu Y, Li X, Xu T, Zhou Z, Zhou K. MODY Probability Calculator Is Suitable for MODY Screening in China: A Population-based Study. *J Endocr Soc* 2024; **8**: bvae047 [PMID: 38562131 DOI: 10.1210/jendso/bvae047]
 - 102 da Silva Santos T, Fonseca L, Santos Monteiro S, Borges Duarte D, Martins Lopes A, Couto de Carvalho A, Oliveira MJ, Borges T, Laranjeira F, Couce ML, Cardoso MH. MODY probability calculator utility in individuals' selection for genetic testing: Its accuracy and performance. *Endocrinol Diabetes Metab* 2022; **5**: e00332 [PMID: 35822264 DOI: 10.1002/edm2.332]
 - 103 De Sousa SMC, Wu KHC, Colclough K, Rawlings L, Dubowsky A, Monnik M, Poplawski N, Scott HS, Horowitz M, Torpy DJ. Identification of monogenic diabetes in an Australian cohort using the Exeter maturity-onset diabetes of the young (MODY) probability calculator and next-generation sequencing gene panel testing. *Acta Diabetol* 2024; **61**: 181-188 [PMID: 37812285 DOI: 10.1007/s00592-023-02193-x]
 - 104 Tarantino RM, Abreu GM, Fonseca ACP, Kupfer R, Pereira MFC, Campos Júnior M, Zajdenverg L, Rodacki M. MODY probability calculator for GCK and HNF1A screening in a multiethnic background population. *Arch Endocrinol Metab* 2020; **64**: 17-23 [PMID: 31576961 DOI: 10.20945/2359-3997000000173]
 - 105 Santomauro AC Jr, Magalhães ÁLF, Motta FT, de Santana LS, Franco PC, de Freitas SM, Sanchez JJD, Costa-Riquetto AD, Teles MG. The performance of the MODY calculator in a non-Caucasian, mixed-race population diagnosed with diabetes mellitus before 35 years of age. *Diabetol Metab Syndr* 2023; **15**: 15 [PMID: 36747290 DOI: 10.1186/s13098-023-00985-3]
 - 106 Ma Y, Gong S, Wang X, Cai X, Xiao X, Gu W, Yang J, Zhong L, Xiao J, Li M, Liu W, Zhang S, Zhou X, Li Y, Zhou L, Zhu Y, Luo Y, Ren Q, Huang X, Gao X, Zhang X, Zhang R, Chen L, Wang F, Wang Q, Hu M, Han X, Ji L. New clinical screening strategy to distinguish HNF1A variant-induced diabetes from young early-onset type 2 diabetes in a Chinese population. *BMJ Open Diabetes Res Care* 2020; **8**: e000745 [PMID: 32238361 DOI: 10.1136/bmjdc-2019-000745]
 - 107 Faguer S, Chassaing N, Bandin F, Prouheze C, Garnier A, Casemayou A, Huart A, Schanstra JP, Calvas P, Decramer S, Chauveau D. The HNF1B score is a simple tool to select patients for HNF1B gene analysis. *Kidney Int* 2014; **86**: 1007-1015 [PMID: 24897035 DOI: 10.1038/ki.2014.202]
 - 108 Isomaa B, Henriksen M, Lehto M, Forsblom C, Karanko S, Sarelin L, Häggblom M, Groop L. Chronic diabetic complications in patients with MODY3 diabetes. *Diabetologia* 1998; **41**: 467-473 [PMID: 9562352 DOI: 10.1007/s001250050931]
 - 109 Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. *Diabet Med* 2009; **26**: 437-441 [PMID: 19388975 DOI: 10.1111/j.1464-5491.2009.02690.x]
 - 110 Naylor RN, Patel KA, Kettunen JLT, Männistö JME, Stoy J, Beltrand J, Polak M, ADA/EASD PMDI, Vilsbøll T, Greeley SAW, Hattersley AT, Tuomi T. Systematic Review of Treatment of Beta-Cell Monogenic Diabetes. *medRxiv* 2023 [PMID: 37214872 DOI: 10.1101/2023.05.12.23289807]
 - 111 Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* 2003; **362**: 1275-1281 [PMID: 14575972 DOI: 10.1016/S0140-6736(03)14571-0]
 - 112 Boileau P, Wolfrum C, Shih DQ, Yang TA, Wolkoff AW, Stoffel M. Decreased glibenclamide uptake in hepatocytes of hepatocyte nuclear factor-1alpha-deficient mice: a mechanism for hypersensitivity to sulfonylurea therapy in patients with maturity-onset diabetes of the young, type 3 (MODY3). *Diabetes* 2002; **51** Suppl 3: S343-S348 [PMID: 12475773 DOI: 10.2337/diabetes.51.2007.s343]
 - 113 Shepherd MH, Shields BM, Hudson M, Pearson ER, Hyde C, Ellard S, Hattersley AT, Patel KA; UNITED study. A UK nationwide prospective study of treatment change in MODY: genetic subtype and clinical characteristics predict optimal glycaemic control after discontinuing insulin and metformin. *Diabetologia* 2018; **61**: 2520-2527 [PMID: 30229274 DOI: 10.1007/s00125-018-4728-6]
 - 114 Christensen MB, Gotfredsen A, Nørgaard K. Efficacy of basal-bolus insulin regimens in the inpatient management of non-critically ill patients with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Metab Res Rev* 2017; **33** [PMID: 28067472 DOI: 10.1002/dmrr.2885]
 - 115 Østoft SH, Bagger JI, Hansen T, Pedersen O, Faber J, Holst JJ, Knop FK, Vilsbøll T. Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. *Diabetes Care* 2014; **37**: 1797-1805 [PMID: 24929431 DOI: 10.2337/dc13-3007]
 - 116 Hohendorff J, Szopa M, Skupien J, Kapusta M, Zapala B, Platek T, Mrozinska S, Parpan T, Glodzik W, Ludwig-Galezowska A, Kiec-Wilk B, Klupa T, Malecki MT. A single dose of dapagliflozin, an SGLT-2 inhibitor, induces higher glycosuria in GCK- and HNF1A-MODY than in type 2 diabetes mellitus. *Endocrine* 2017; **57**: 272-279 [PMID: 28593615 DOI: 10.1007/s12020-017-1341-2]
 - 117 Pruhova S, Dusatkova P, Neumann D, Hollay E, Cinek O, Lebl J, Sumnik Z. Two cases of diabetic ketoacidosis in HNF1A-MODY linked to severe dehydration: is it time to change the diagnostic criteria for MODY? *Diabetes Care* 2013; **36**: 2573-2574 [PMID: 23610083 DOI: 10.2337/dc13-0058]
 - 118 Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. *Diabetes Care* 2011; **34**: 1878-1884 [PMID: 21788644 DOI: 10.2337/dc11-0035]
 - 119 Dickens LT, Naylor RN. Clinical Management of Women with Monogenic Diabetes During Pregnancy. *Curr Diab Rep* 2018; **18**: 12 [PMID: 29450745 DOI: 10.1007/s11892-018-0982-8]
 - 120 Timsit J, Ciangura C, Dubois-Laforgue D, Saint-Martin C, Bellanne-Chantelot C. Pregnancy in Women With Monogenic Diabetes due to Pathogenic Variants of the Glucokinase Gene: Lessons and Challenges. *Front Endocrinol (Lausanne)* 2021; **12**: 802423 [PMID: 35069449 DOI: 10.3389/fendo.2021.802423]
 - 121 Jeeyavudeen MS, Murray SR, Strachan MWJ. Management of monogenic diabetes in pregnancy: A narrative review. *World J Diabetes* 2024;

- 15: 15-23 [PMID: 38313847 DOI: 10.4239/wjd.v15.i1.15]
- 122 **Caswell RC**, Snowsill T, Houghton JAL, Chakera AJ, Shepherd MH, Laver TW, Knight BA, Wright D, Hattersley AT, Ellard S. Noninvasive Fetal Genotyping by Droplet Digital PCR to Identify Maternally Inherited Monogenic Diabetes Variants. *Clin Chem* 2020; **66**: 958-965 [PMID: 32533152 DOI: 10.1093/clinchem/hvaa104]
- 123 **Rudland VL**. Diagnosis and management of glucokinase monogenic diabetes in pregnancy: current perspectives. *Diabetes Metab Syndr Obes* 2019; **12**: 1081-1089 [PMID: 31372018 DOI: 10.2147/DMSO.S186610]
- 124 **Johnson MB**, Patel KA, De Franco E, Hagopian W, Killian M, McDonald TJ, Tree TIM, Domingo-Vila C, Hudson M, Hammersley S, Dobbs R; EXE-T1D Consortium, Ellard S, Flanagan SE, Hattersley AT, Oram RA. Type 1 diabetes can present before the age of 6 months and is characterised by autoimmunity and rapid loss of beta cells. *Diabetologia* 2020; **63**: 2605-2615 [PMID: 33029656 DOI: 10.1007/s00125-020-05276-4]
- 125 **von Mühlendahl KE**, Herkenhoff H. Long-term course of neonatal diabetes. *N Engl J Med* 1995; **333**: 704-708 [PMID: 7637748 DOI: 10.1056/NEJM199509143331105]
- 126 **Busiah K**, Drunat S, Vaivre-Douret L, Bonnefond A, Simon A, Flechtner I, Gérard B, Pouvreau N, Elie C, Nimri R, De Vries L, Tubiana-Rufi N, Metz C, Bertrand AM, Nivot-Adamiak S, de Kerdanet M, Stuckens C, Jennane F, Souchon PF, Le Tallec C, Désirée C, Pereira S, Dechaume A, Robert JJ, Phillip M, Scharfmann R, Czernichow P, Froguel P, Vaxillaire M, Polak M, Cavé H; French NDM study group. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study [corrected]. *Lancet Diabetes Endocrinol* 2013; **1**: 199-207 [PMID: 24622368 DOI: 10.1016/S2213-8587(13)70059-7]
- 127 **Hashimoto Y**, Dateki S, Hirose M, Satomura K, Sawada H, Mizuno H, Sugihara S, Maruyama K, Urakami T, Sugawara H, Shirai K, Yorifuji T. Molecular and clinical features of K(ATP) -channel neonatal diabetes mellitus in Japan. *Pediatr Diabetes* 2017; **18**: 532-539 [PMID: 27681997 DOI: 10.1111/pedi.12447]
- 128 **Letourneau LR**, Carmody D, Wroblewski K, Denson AM, Sanyoua M, Naylor RN, Philipson LH, Greeley SAW. Diabetes Presentation in Infancy: High Risk of Diabetic Ketoacidosis. *Diabetes Care* 2017; **40**: e147-e148 [PMID: 28779000 DOI: 10.2337/dc17-1145]
- 129 **Svalastoga P**, Sulen Å, Fehn JR, Aukland SM, Irgens H, Sirnes E, Fevang SKE, Valen E, Elgen IB, Njølstad PR. Intellectual Disability in K(ATP) Channel Neonatal Diabetes. *Diabetes Care* 2020; **43**: 526-533 [PMID: 31932458 DOI: 10.2337/dc19-1013]
- 130 **Polak M**, Dechaume A, Cavé H, Nimri R, Crosnier H, Sulmont V, de Kerdanet M, Scharfmann R, Lebenthal Y, Froguel P, Vaxillaire M; French ND (Neonatal Diabetes) Study Group. Heterozygous missense mutations in the insulin gene are linked to permanent diabetes appearing in the neonatal period or in early infancy: a report from the French ND (Neonatal Diabetes) Study Group. *Diabetes* 2008; **57**: 1115-1119 [PMID: 18171712 DOI: 10.2337/db07-1358]
- 131 **Bowman P**, Sulen Å, Barbetti F, Beltrand J, Svalastoga P, Codner E, Tessmann EH, Juliusson PB, Skrivarhaug T, Pearson ER, Flanagan SE, Babiker T, Thomas NJ, Shepherd MH, Ellard S, Klimes I, Szopa M, Polak M, Iafusco D, Hattersley AT, Njølstad PR; Neonatal Diabetes International Collaborative Group. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. *Lancet Diabetes Endocrinol* 2018; **6**: 637-646 [PMID: 29880308 DOI: 10.1016/S2213-8587(18)30106-2]
- 132 **Babiker T**, Vedovato N, Patel K, Thomas N, Finn R, Männikkö R, Chakera AJ, Flanagan SE, Shepherd MH, Ellard S, Ashcroft FM, Hattersley AT. Successful transfer to sulfonylureas in KCNJ11 neonatal diabetes is determined by the mutation and duration of diabetes. *Diabetologia* 2016; **59**: 1162-1166 [PMID: 27033559 DOI: 10.1007/s00125-016-3921-8]
- 133 **Cavé H**, Polak M, Drunat S, Denamur E, Czernichow P. Refinement of the 6q chromosomal region implicated in transient neonatal diabetes. *Diabetes* 2000; **49**: 108-113 [PMID: 10615957 DOI: 10.2337/diabetes.49.1.108]
- 134 **Gardner RJ**, Mackay DJ, Mungall AJ, Polychronakos C, Siebert R, Shield JP, Temple IK, Robinson DO. An imprinted locus associated with transient neonatal diabetes mellitus. *Hum Mol Genet* 2000; **9**: 589-596 [PMID: 10699182 DOI: 10.1093/hmg/9.4.589]
- 135 **Hoffmann A**, Spengler D. Role of ZAC1 in transient neonatal diabetes mellitus and glucose metabolism. *World J Biol Chem* 2015; **6**: 95-109 [PMID: 26322169 DOI: 10.4331/wjbc.v6.i3.95]
- 136 **Arima T**, Drewell RA, Arney KL, Inoue J, Makita Y, Hata A, Oshimura M, Wake N, Surani MA. A conserved imprinting control region at the HYMAI/ZAC domain is implicated in transient neonatal diabetes mellitus. *Hum Mol Genet* 2001; **10**: 1475-1483 [PMID: 11448939 DOI: 10.1093/hmg/10.14.1475]
- 137 **Gloyn AL**, Reimann F, Girard C, Edghill EL, Proks P, Pearson ER, Temple IK, Mackay DJ, Shield JP, Freedenberg D, Noyes K, Ellard S, Ashcroft FM, Gribble FM, Hattersley AT. Relapsing diabetes can result from moderately activating mutations in KCNJ11. *Hum Mol Genet* 2005; **14**: 925-934 [PMID: 15718250 DOI: 10.1093/hmg/ddi086]
- 138 **Pezzino G**, Ruta R, Rapini N, Chiodo DC, Mucciolo M, Tomaselli L, Cianfarani S, Barbetti F. A rare cause of transient neonatal diabetes mellitus: Spontaneous HNF1B splice variant. *Diabet Med* 2024; **41**: e15202 [PMID: 37597176 DOI: 10.1111/dme.15202]
- 139 **Patch AM**, Flanagan SE, Boustred C, Hattersley AT, Ellard S. Mutations in the ABCC8 gene encoding the SUR1 subunit of the KATP channel cause transient neonatal diabetes, permanent neonatal diabetes or permanent diabetes diagnosed outside the neonatal period. *Diabetes Obes Metab* 2007; **9** Suppl 2: 28-39 [PMID: 17919176 DOI: 10.1111/j.1463-1326.2007.00772.x]
- 140 **Bonfanti R**, Iafusco D, Rabbone I, Diedenhofen G, Bizzarri C, Patera PI, Reinstadler P, Costantino F, Calcaterra V, Iughetti L, Savastio S, Favia A, Cardella F, Lo Presti D, Girtler Y, Rabbiosi S, D'Annunzio G, Zanfardino A, Piscopo A, Casaburo F, Pintomalli L, Russo L, Grasso V, Minuto N, Mucciolo M, Novelli A, Marucci A, Piccini B, Toni S, Silvestri F, Carrera P, Rigamonti A, Frontino G, Trada M, Tinti D, Delvecchio M, Rapini N, Schiaffini R, Mammi C, Barbetti F; Diabetes Study Group of ISPED. Differences between transient neonatal diabetes mellitus subtypes can guide diagnosis and therapy. *Eur J Endocrinol* 2021; **184**: 575-585 [PMID: 33606663 DOI: 10.1530/EJE-20-1030]
- 141 **Yorifuji T**, Matsubara K, Sakakibara A, Hashimoto Y, Kawakita R, Hosokawa Y, Fujimaru R, Murakami A, Tamagawa N, Hatake K, Nagasaka H, Suzuki J, Urakami T, Izawa M, Kagami M. Abnormalities in chromosome 6q24 as a cause of early-onset, non-obese, non-autoimmune diabetes mellitus without history of neonatal diabetes. *Diabet Med* 2015; **32**: 963-967 [PMID: 25809823 DOI: 10.1111/dme.12758]
- 142 **Docherty LE**, Kabwama S, Lehmann A, Hawke E, Harrison L, Flanagan SE, Ellard S, Hattersley AT, Shield JP, Ennis S, Mackay DJ, Temple IK. Clinical presentation of 6q24 transient neonatal diabetes mellitus (6q24 TNDM) and genotype-phenotype correlation in an international cohort of patients. *Diabetologia* 2013; **56**: 758-762 [PMID: 23385738 DOI: 10.1007/s00125-013-2832-1]
- 143 **Gunes SO**, Calisici E, Arslan M, Akin O, Karagol BS. Transient Neonatal Diabetes Mellitus and Seizure with an Unknown Etiology. *J Pediatr Genet* 2023; **12**: 242-245 [PMID: 37575648 DOI: 10.1055/s-0041-1727175]
- 144 **Johnson MB**, Hattersley AT, Flanagan SE. Monogenic autoimmune diseases of the endocrine system. *Lancet Diabetes Endocrinol* 2016; **4**: 862-872 [PMID: 27474216 DOI: 10.1016/S2213-8587(16)30095-X]

- 145 **Strakova V**, Elblova L, Johnson MB, Dusatkova P, Obermannova B, Petruzelkova L, Kolouskova S, Snajderova M, Fronkova E, Svaton M, Lebl J, Hattersley AT, Sumnik Z, Pruhova S. Screening of monogenic autoimmune diabetes among children with type 1 diabetes and multiple autoimmune diseases: is it worth doing? *J Pediatr Endocrinol Metab* 2019; **32**: 1147-1153 [PMID: 31483759 DOI: 10.1515/jpem-2019-0261]
- 146 **Hossen MM**, Ma Y, Yin Z, Xia Y, Du J, Huang JY, Huang JJ, Zou L, Ye Z, Huang Z. Current understanding of CTLA-4: from mechanism to autoimmune diseases. *Front Immunol* 2023; **14**: 1198365 [PMID: 37497212 DOI: 10.3389/fimmu.2023.1198365]
- 147 **Kleine-Eggebrecht N**, Staufner C, Kathemann S, Elgizouli M, Kopajtich R, Prokisch H, Linka E. Mutation in ITCH Gene Can Cause Syndromic Multisystem Autoimmune Disease With Acute Liver Failure. *Pediatrics* 2019; **143**: e20181554 [PMID: 30705142 DOI: 10.1542/peds.2018-1554]
- 148 **Borysewicz-Sańczyk H**, Sawicka B, Wawrusiewicz-Kurylonek N, Głowińska-Olszewska B, Kadłubiska A, Gościk J, Szadkowska A, Łosiewicz A, Młynarski W, Kretowski A, Bossowski A. Genetic Association Study of IL2RA, IFIH1, and CTLA-4 Polymorphisms With Autoimmune Thyroid Diseases and Type 1 Diabetes. *Front Pediatr* 2020; **8**: 481 [PMID: 32974248 DOI: 10.3389/fped.2020.00481]
- 149 **Kardelen AD**, Kara M, Güller D, Özturan EK, Abalı ZY, Ceylaner S, Kıyıkım A, Cantez S, Torun SH, Poyrazoglu S, Bas F, Darendeliler F. LRBA deficiency: a rare cause of type 1 diabetes, colitis, and severe immunodeficiency. *Hormones (Athens)* 2021; **20**: 389-394 [PMID: 33155142 DOI: 10.1007/s42000-020-00257-z]
- 150 **Murphy R**, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. *Diabet Med* 2008; **25**: 383-399 [PMID: 18294221 DOI: 10.1111/j.1464-5491.2008.02359.x]
- 151 **Koenig MK**. Presentation and diagnosis of mitochondrial disorders in children. *Pediatr Neurol* 2008; **38**: 305-313 [PMID: 18410845 DOI: 10.1016/j.pediatrneurol.2007.12.001]
- 152 **Hu T**, Chitnis N, Monos D, Dinh A. Next-generation sequencing technologies: An overview. *Hum Immunol* 2021; **82**: 801-811 [PMID: 33745759 DOI: 10.1016/j.humimm.2021.02.012]
- 153 **Pareek CS**, Smoczynski R, Tretyn A. Sequencing technologies and genome sequencing. *J Appl Genet* 2011; **52**: 413-435 [PMID: 21698376 DOI: 10.1007/s13353-011-0057-x]
- 154 **Ellard S**, Lango Allen H, De Franco E, Flanagan SE, Hysenaj G, Colclough K, Houghton JA, Shepherd M, Hattersley AT, Weedon MN, Caswell R. Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. *Diabetologia* 2013; **56**: 1958-1963 [PMID: 23771172 DOI: 10.1007/s00125-013-2962-5]
- 155 **Zmysłowska A**, Jakiel P, Gadzalska K, Majos A, Płoszaj T, Ben-Skowronek I, Deja G, Glowinska-Olszewska B, Jarosz-Chobot P, Klonowska B, Kowalska I, Młynarski W, Mysliwiec M, Nazim J, Noczynska A, Robak-Kontna K, Skala-Zamorowska E, Skowronska B, Szadkowska A, Szypowska A, Walczak M, Borowiec M. Next-generation sequencing is an effective method for diagnosing patients with different forms of monogenic diabetes. *Diabetes Res Clin Pract* 2022; **183**: 109154 [PMID: 34826540 DOI: 10.1016/j.diabetes.2021.109154]
- 156 **Kheriji N**, Dallali H, Gouiza I, Hechmi M, Mahjoub F, Mrad M, Krir A, Soltani M, Trabelsi H, Hamdi W, Bahlous A, Ben Ahmed M, Jamoussi H, Kefi R. Whole-exome sequencing reveals novel variants of monogenic diabetes in Tunisia: impact on diagnosis and healthcare management. *Front Genet* 2023; **14**: 1224284 [PMID: 38162681 DOI: 10.3389/fgene.2023.1224284]
- 157 **Misra S**, Shields B, Colclough K, Johnston DG, Oliver NS, Ellard S, Hattersley AT. South Asian individuals with diabetes who are referred for MODY testing in the UK have a lower mutation pick-up rate than white European people. *Diabetologia* 2016; **59**: 2262-2265 [PMID: 27435864 DOI: 10.1007/s00125-016-4056-7]
- 158 **Xue Y**, Ankala A, Wilcox WR, Hegde MR. Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. *Genet Med* 2015; **17**: 444-451 [PMID: 25232854 DOI: 10.1038/gim.2014.122]
- 159 **Johansson S**, Irgens H, Chudasama KK, Molnes J, Aerts J, Roque FS, Jonassen I, Levy S, Lima K, Knappskog PM, Bell GI, Molven A, Njolstad PR. Exome sequencing and genetic testing for MODY. *PLoS One* 2012; **7**: e38050 [PMID: 22662265 DOI: 10.1371/journal.pone.0038050]
- 160 **Ali Khan I**. Do second generation sequencing techniques identify documented genetic markers for neonatal diabetes mellitus? *Heliyon* 2021; **7**: e07903 [PMID: 34584998 DOI: 10.1016/j.heliyon.2021.e07903]
- 161 **Özdemir TR**, Kırbıyık Ö, Dündar BN, Abacı A, Kaya ÖÖ, Çatlı G, Özyılmaz B, Acar S, Koç A, Güvenç MS, Kutbay YB, Erdoğan KM. Targeted next generation sequencing in patients with maturity-onset diabetes of the young (MODY). *J Pediatr Endocrinol Metab* 2018; **31**: 1295-1304 [PMID: 30447144 DOI: 10.1515/jpem-2018-0184]
- 162 **Aydogan HY**, Gul N, Demirci DK, Mutlu U, Gulfidan G, Arga KY, Ozder A, Camli AA, Tutuncu Y, Ozturk O, Cacina C, Darendeliler F, Poyrazoglu S, Satman I. Precision Diagnosis of Maturity-Onset Diabetes of the Young with Next-Generation Sequencing: Findings from the MODY-IST Study in Adult Patients. *OMICS* 2022; **26**: 218-235 [PMID: 35333605 DOI: 10.1089/omi.2022.0006]
- 163 **Donath X**, Saint-Martin C, Dubois-Laforgue D, Rajasingham R, Mifsud F, Ciangura C, Timsit J, Bellanné-Chantelot C; Monogenic Diabetes Study Group of the Société Francophone du Diabète. Next-generation sequencing identifies monogenic diabetes in 16% of patients with late adolescence/adult-onset diabetes selected on a clinical basis: a cross-sectional analysis. *BMC Med* 2019; **17**: 132 [PMID: 31291970 DOI: 10.1186/s12916-019-1363-0]
- 164 **Sztromwasser P**, Michalak A, Małachowska B, Młodzik P, Antosik K, Hogendorf A, Zmysłowska A, Borowiec M, Młynarski W, Fendler W. A cross-sectional study of patients referred for HNF1B-MODY genetic testing due to cystic kidneys and diabetes. *Pediatr Diabetes* 2020; **21**: 422-430 [PMID: 31825128 DOI: 10.1111/pedi.12959]
- 165 **Dotto RP**, Mathez ALG, Franco LF, de Sá JR, Weinert LS, Silveiro SP, de Mello Almada Giuffrida F, da Silva MRD, Reis AF. Improving the identification of mody mutations by using mlpa technique in the molecular diagnostics routine. *Diabetol Metab Syndr* 2015; **7**: A246 [DOI: 10.1186/1758-5996-7-s1-a246]
- 166 **Loos MA**, Gomez G, Mayorga L, Caraballo RH, Eiroa HD, Obregon MG, Rugilo C, Lubieniecki F, Taratuto AL, Saccoliti M, Alonso CN, Araújo HV. Clinical and molecular characterization of mitochondrial DNA disorders in a group of Argentinian pediatric patients. *Mol Genet Metab Rep* 2021; **27**: 100733 [PMID: 33717984 DOI: 10.1016/j.ymgmr.2021.100733]
- 167 **Lavrichenko K**, Johansson S, Jonassen I. Comprehensive characterization of copy number variation (CNV) called from array, long- and short-read data. *BMC Genomics* 2021; **22**: 826 [PMID: 34789167 DOI: 10.1186/s12864-021-08082-3]
- 168 **Berberich AJ**, Wang J, Cao H, McIntyre AD, Spaic T, Miller DB, Stock S, Huot C, Stein R, Knoll J, Yang P, Robinson JF, Hegele RA. Simplifying Detection of Copy-Number Variations in Maturity-Onset Diabetes of the Young. *Can J Diabetes* 2021; **45**: 71-77 [PMID: 33011132 DOI: 10.1016/j.cjcd.2020.06.001]
- 169 **Berberich AJ**, Huot C, Cao H, McIntyre AD, Robinson JF, Wang J, Hegele RA. Copy Number Variation in GCK in Patients With Maturity-

- Onset Diabetes of the Young. *J Clin Endocrinol Metab* 2019; **104**: 3428-3436 [PMID: 30912798 DOI: 10.1210/jc.2018-02574]
- 170 **Yan JB**, Zhang R, Xiong C, Hu C, Lv Y, Wang CR, Jia WP, Zeng F. Pyrosequencing is an accurate and reliable method for the analysis of heteroplasmy of the A3243G mutation in patients with mitochondrial diabetes. *J Mol Diagn* 2014; **16**: 431-439 [PMID: 24803323 DOI: 10.1016/j.jmoldx.2014.03.005]
- 171 **Touati A**, Errea-Dorronsoro J, Nouri S, Halleb Y, Pereda A, Mahdhaoui N, Ghith A, Saad A, Perez de Nanclares G, H'mida Ben Brahim D. Transient neonatal diabetes mellitus and hypomethylation at additional imprinted loci: novel ZFP57 mutation and review on the literature. *Acta Diabetol* 2019; **56**: 301-307 [PMID: 30315371 DOI: 10.1007/s00592-018-1239-3]
- 172 **Temple IK**, Mackay DJ. Diabetes Mellitus, 6q24-Related Transient Neonatal. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editor. GeneReviews®. Seattle (WA): University of Washington, Seattle 1993 [PMID: 20301706]
- 173 **Pang L**, Colclough KC, Shepherd MH, McLean J, Pearson ER, Ellard S, Hattersley AT, Shields BM. Improvements in Awareness and Testing Have Led to a Threefold Increase Over 10 Years in the Identification of Monogenic Diabetes in the U.K. *Diabetes Care* 2022; **45**: 642-649 [PMID: 35061023 DOI: 10.2337/dc21-2056]
- 174 **Stanik J**, Kusekova M, Huckova M, Valentinova L, Masindova I, Stanikova D, Ferenczova J, Gasperikova D, Klimes I. Impact of Type 2 diabetes on Glucokinase diabetes (GCK-MODY) phenotype in a Roma (Gypsy) family - case report. *Endocr Regul* 2012; **46**: 99-105 [PMID: 22540858 DOI: 10.4149/endo_2012_02_99]
- 175 **Kwak SH**, Jung CH, Ahn CH, Park J, Chae J, Jung HS, Cho YM, Lee DH, Kim JI, Park KS. Clinical whole exome sequencing in early onset diabetes patients. *Diabetes Res Clin Pract* 2016; **122**: 71-77 [PMID: 27810688 DOI: 10.1016/j.diabres.2016.10.005]
- 176 **Zhang H**, Colclough K, Gloy AL, Pollin TI. Monogenic diabetes: a gateway to precision medicine in diabetes. *J Clin Invest* 2021; **131**: e142244 [PMID: 33529164 DOI: 10.1172/JCI142244]
- 177 **Burke W**, Parens E, Chung WK, Berger SM, Appelbaum PS. The Challenge of Genetic Variants of Uncertain Clinical Significance : A Narrative Review. *Ann Intern Med* 2022; **175**: 994-1000 [PMID: 35436152 DOI: 10.7326/M21-4109]
- 178 **Richards S**, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; **17**: 405-424 [PMID: 25741868 DOI: 10.1038/gim.2015.30]
- 179 **Rehm HL**, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, Ledbetter DH, Maglott DR, Martin CL, Nussbaum RL, Plon SE, Ramos EM, Sherry ST, Watson MS; ClinGen. ClinGen--the Clinical Genome Resource. *N Engl J Med* 2015; **372**: 2235-2242 [PMID: 26014595 DOI: 10.1056/NEJMs1406261]
- 180 **ClinGen**. Monogenic Diabetes Gene Curation Expert Panel. [cited March 04, 2025]. Available from: <https://clinicalgenome.org/affiliation/40016/>
- 181 **ClinGen**. Monogenic Diabetes Variant Curation Expert Panel. [cited March 04, 2025]. Available from: <https://clinicalgenome.org/affiliation/50016/>
- 182 **Misra S**, Owen KR. Genetics of Monogenic Diabetes: Present Clinical Challenges. *Curr Diab Rep* 2018; **18**: 141 [PMID: 30377832 DOI: 10.1007/s11892-018-1111-4]
- 183 **MacArthur DG**, Manolio TA, Dimmock DP, Rehm HL, Shendure J, Abecasis GR, Adams DR, Altman RB, Antonarakis SE, Ashley EA, Barrett JC, Biesecker LG, Conrad DF, Cooper GM, Cox NJ, Daly MJ, Gerstein MB, Goldstein DB, Hirschhorn JN, Leal SM, Pennacchio LA, Stamatoiyannopoulos JA, Sunyaev SR, Valle D, Voight BF, Winckler W, Gunter C. Guidelines for investigating causality of sequence variants in human disease. *Nature* 2014; **508**: 469-476 [PMID: 24759409 DOI: 10.1038/nature13127]
- 184 **Peixoto-Barbosa R**, Calliari LE, Crispim F, Moisés RS, Dib SA, Reis AF, Giuffrida FMA. Clinical screening for GCK-MODY in 2,989 patients from the Brazilian Monogenic Diabetes Study Group (BRASMOD) and the Brazilian Type 1 Diabetes Study Group (BrazDiab1SG). *Arch Endocrinol Metab* 2024; **68**: e230314 [PMID: 39420902 DOI: 10.20945/2359-4292-2023-0314]
- 185 **Ushijima K**, Narumi S, Ogata T, Yokota I, Sugihara S, Kaname T, Horikawa Y, Matsubara Y, Fukami M, Kawamura T; Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes. KLF11 variant in a family clinically diagnosed with early childhood-onset type 1B diabetes. *Pediatr Diabetes* 2019; **20**: 712-719 [PMID: 31124255 DOI: 10.1111/pedi.12868]
- 186 **Stankute I**, Kazlauskienė M, Blouin JL, Schwitzgebel VM, Verkauskienė R. Co-segregation analysis and functional trial in vivo of candidate genes for monogenic diabetes. *BMJ Open Diabetes Res Care* 2022; **10** [PMID: 36585034 DOI: 10.1136/bmjdr-2022-003038]
- 187 **Ascencio-Carbajal T**, Saruwatari-Zavala G, Navarro-Garcia F, Frixione E. Genetic/genomic testing: defining the parameters for ethical, legal and social implications (ELSI). *BMC Med Ethics* 2021; **22**: 156 [PMID: 34814901 DOI: 10.1186/s12910-021-00720-5]
- 188 **Ferreira A**, Gotschall JW, Grant-Kels JM. Ethical concerns of direct-to-consumer genetic testing. *J Am Acad Dermatol* 2024; **90**: 1117-1118 [PMID: 37024050 DOI: 10.1016/j.jaad.2023.03.044]
- 189 **Xue Y**, Chen Y, Ayub Q, Huang N, Ball EV, Mort M, Phillips AD, Shaw K, Stenson PD, Cooper DN, Tyler-Smith C; 1000 Genomes Project Consortium. Deleterious- and disease-allele prevalence in healthy individuals: insights from current predictions, mutation databases, and population-scale resequencing. *Am J Hum Genet* 2012; **91**: 1022-1032 [PMID: 23217326 DOI: 10.1016/j.ajhg.2012.10.015]
- 190 **He B**, Li X, Zhou Z. Continuous spectrum of glucose dysmetabolism due to the KCNJ11 gene mutation-Case reports and review of the literature. *J Diabetes* 2021; **13**: 19-32 [PMID: 32935446 DOI: 10.1111/1753-0407.13114]
- 191 **Heller S**, Melzer MK, Azoitei N, Julier C, Kleger A. Human Pluripotent Stem Cells Go Diabetic: A Glimpse on Monogenic Variants. *Front Endocrinol (Lausanne)* 2021; **12**: 648284 [PMID: 34079523 DOI: 10.3389/fendo.2021.648284]
- 192 **Burgos JI**, Vallier L, Rodríguez-Seguí SA. Monogenic Diabetes Modeling: In Vitro Pancreatic Differentiation From Human Pluripotent Stem Cells Gains Momentum. *Front Endocrinol (Lausanne)* 2021; **12**: 692596 [PMID: 34295307 DOI: 10.3389/fendo.2021.692596]
- 193 **Tung JY**, Boodhansingh K, Stanley CA, De León DD. Clinical heterogeneity of hyperinsulinism due to HNF1A and HNF4A mutations. *Pediatr Diabetes* 2018; **19**: 910-916 [PMID: 29493090 DOI: 10.1111/pedi.12655]
- 194 **Juszcak A**, Pryse R, Schuman A, Owen KR. When to consider a diagnosis of MODY at the presentation of diabetes: aetiology matters for correct management. *Br J Gen Pract* 2016; **66**: e457-e459 [PMID: 27231307 DOI: 10.3399/bjgp16X685537]



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