

REVIEW ARTICLE

Maturity-onset diabetes of the young and related monogenic diabetes: molecular mechanisms, genotype-directed treatment, and diagnostic pathways

Kehinde Sowunmi^{1,2} 

ABSTRACT

Background: Maturity-onset diabetes of the young (MODY) is the most common form of monogenic diabetes, with 50%-90% of cases initially misclassified as type 1 or type 2 diabetes. Genetic diagnosis enables individualized treatment.

Objective: To synthesize evidence on molecular mechanisms, clinical phenotypes, diagnostic pathways, and genotype-directed treatment for MODY and related monogenic diabetes, including HNF1B-MODY and KCNJ11/ABCC8-related permanent neonatal diabetes mellitus (PNDM).

Methods: PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science were searched from inception to 30 June 2026. Eligible publications included English-language primary studies, systematic reviews, meta-analyses, and guidelines. Small case reports, non-human studies, and unavailable full texts were excluded. One reviewer conducted study selection and data extraction. Overall, 120 primary studies and 15 secondary reviews/guidelines were included. Methodological quality was assessed using the Newcastle–Ottawa Scale, Cochrane Risk of Bias tool, and AMSTAR-2. Findings were synthesized narratively.

Results: HNF1A, GCK, and HNF4A account for most MODY diagnoses in European cohorts, although frequencies vary across populations. HNF1A- and HNF4A-MODY respond to low-dose sulfonylureas, whereas GCK-MODY generally requires no pharmacotherapy. HNF1B-MODY involves multisystem disease and generally responds poorly to sulfonylureas. KCNJ11/ABCC8-related PNDM, distinct from MODY, may respond to high-dose sulfonylureas. Autoantibody status, C-peptide preservation, and family history guide genetic testing. Evidence was predominantly observational and of moderate quality, with only one randomized trial.

Conclusion: Genetic diagnosis supports precision treatment, including sulfonylurea transition, insulin avoidance, and pregnancy-specific management. Expanding genetic testing access, particularly in resource-constrained settings, and strengthening evidence across diverse populations remain priorities.

Keywords: MODY, monogenic diabetes, HNF1A, GCK, HNF4A, HNF1B, sulfonylurea, neonatal diabetes, genetic testing, precision medicine, systematic review.

Introduction

Diabetes mellitus comprises a heterogeneous group of metabolic disorders unified by chronic hyperglycemia but divergent in etiology, pathophysiology, and therapeutic requirements (1–3). While T1D and T2D constitute the vast majority of cases, monogenic forms of diabetes, caused by highly penetrant variants in single genes, account for approximately 1%-3% of all diabetes diagnoses, with maturity-onset diabetes of the young

Correspondence to: Kehinde Sowunmi

*Department of Biological Science, Tai Solarin Federal University of Education, Ijebu Ode, Nigeria and Department of Cell Biology and Genetics, University of Lagos, Lagos, Nigeria.

Email: sowunmikehinde111@gmail.com

Full list of author information is available at the end of the article.

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(MODY) representing the largest subgroup (4,5). Despite its relative frequency, MODY remains substantially underdiagnosed, with current estimates indicating that 50%-90% of cases are misclassified as T1D or T2D, resulting in diagnostic delays frequently exceeding 10 years (6,7).

The clinical consequences of misdiagnosis are considerable. Patients erroneously classified as T1D may undergo years of unnecessary insulin therapy with attendant hypoglycemia risk, psychological burden, and healthcare costs. Conversely, patients misdiagnosed as T2D may receive metformin or other agents with limited efficacy in specific MODY subtypes, while the optimal therapy, often an inexpensive sulfonylurea, remains unutilized. Genetic confirmation of MODY not only resolves diagnostic uncertainty but also enables cascade testing of at-risk relatives and directs genotype-specific therapeutic decision-making (8,4).

This systematic review addresses three objectives: (i) to delineate the molecular mechanisms and clinical phenotypes of the major MODY subtypes and related monogenic diabetes forms; (ii) to provide evidence-based, genotype-specific treatment algorithms grounded in molecular pathophysiology; and (iii) to examine diagnostic pathways, including strategies for resource-limited settings where genetic testing access remains restricted.

The scope of this review encompasses MODY and permanent neonatal diabetes mellitus (PNDM) caused by KCNJ11 and ABCC8 mutations. Although PNDM is not classified as MODY - which by definition presents after 6 months of age and typically during adolescence or young adulthood - it is included because: (i) it shares the fundamental characteristic of monogenic etiology; (ii) it exemplifies the principle of genotype-directed therapy, specifically the efficacy of high-dose sulfonylureas; and (iii) it is routinely included in the differential diagnosis and genetic testing panels used for young-onset monogenic diabetes.

Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (9). The review protocol was not prospectively registered in PROSPERO or another registry; this is acknowledged as a methodological limitation.

Search strategy

A systematic literature search was conducted across four electronic databases: PubMed/MEDLINE (via NCBI), Embase (via Elsevier), Cochrane Library (CENTRAL and CDSR), and Web of Science Core Collection, encompassing records from database inception through 30 June 2026. The exact search date for each database was 30 June 2026. Database-specific search strategies are provided in Supplementary Material 1.

The search strategy combined Medical Subject Headings (MeSH) and Emtree terms with free-text keywords. The core search concepts were as follows: (i) monogenic

diabetes/MODY; (ii) specific gene names; and (iii) treatment, diagnosis, or genetic testing. No language restrictions were applied during the initial search; only English-language full-text articles were included in the final synthesis.

PubMed/MEDLINE search strategy: #1 “Diabetes Mellitus”[MeSH] OR “Diabetes Mellitus, Type 2”[MeSH] OR “Diabetes Mellitus, Type 1”[MeSH] #2 “maturity-onset diabetes of the young”[Title/Abstract] OR MODY[Title/Abstract] OR “monogenic diabetes”[Title/Abstract] #3 HNF1A[Title/Abstract] OR GCK[Title/Abstract] OR HNF4A[Title/Abstract] OR HNF1B[Title/Abstract] OR KCNJ11[Title/Abstract] OR ABCC8[Title/Abstract] OR PDX1[Title/Abstract] OR NEUROD1[Title/Abstract] #4 sulfonylurea*[Title/Abstract] OR treatment[Title/Abstract] OR diagnosis[Title/Abstract] OR “genetic testing”[Title/Abstract] OR “neonatal diabetes”[Title/Abstract] #5 #2 AND #3 AND #4 #6 #5 NOT (“animals”[MeSH Terms] NOT “humans”[MeSH Terms])

Embase search strategy: #1 “diabetes mellitus”/exp OR “diabetes mellitus, type 2”/exp OR “diabetes mellitus, type 1”/exp #2 “maturity onset diabetes of the young”:ti,ab OR mody:ti,ab OR “monogenic diabetes”:ti,ab #3 hnf1a:ti,ab OR gck:ti,ab OR hnf4a:ti,ab OR hnf1b:ti,ab OR knj11:ti,ab OR abcc8:ti,ab OR pdx1:ti,ab OR neurod1:ti,ab #4 sulfonylurea*:ti,ab OR treatment:ti,ab OR diagnosis:ti,ab OR “genetic testing”:ti,ab OR “neonatal diabetes”:ti,ab #5 #2 AND #3 AND #4 #6 #5 NOT (“animal”/exp NOT “human”/exp)

Cochrane Library search strategy: [mh “Diabetes Mellitus”] OR [mh “Diabetes Mellitus, Type 2”] OR [mh “Diabetes Mellitus, Type 1”] AND (“maturity-onset diabetes of the young” OR MODY OR “monogenic diabetes”):ti,ab,kw AND (HNF1A OR GCK OR HNF4A OR HNF1B OR KCNJ11 OR ABCC8):ti,ab,kw AND (sulfonylurea* OR treatment OR diagnosis OR “genetic testing” OR “neonatal diabetes”):ti,ab,kw

Web of Science search strategy: TS=(“maturity-onset diabetes of the young” OR MODY OR “monogenic diabetes”) AND TS=(HNF1A OR GCK OR HNF4A OR HNF1B OR KCNJ11 OR ABCC8 OR PDX1 OR NEUROD1) AND TS=(sulfonylurea* OR treatment OR diagnosis OR “genetic testing” OR “neonatal diabetes”) NOT TS=(animal* NOT human*).

Additional records were identified through manual screening of reference lists of included articles and relevant systematic reviews and through searches of clinical trial registers (ClinicalTrials.gov, WHO ICTRP).

Inclusion and exclusion criteria

Inclusion criteria included: (i) peer-reviewed original research articles, systematic reviews, meta-analyses, and clinical practice guidelines; (ii) studies reporting on molecular genetics, clinical phenotypes, diagnostic accuracy, or treatment outcomes in MODY or related monogenic diabetes; and (iii) studies with clearly defined patient populations and reproducible methodology.

Exclusion criteria included: (i) case reports describing fewer than three patients; (ii) non-human or *in vitro*

studies without clinical correlation; (iii) editorials, commentaries, and opinion pieces lacking primary data; (iv) conference abstracts without subsequent peer-reviewed publication; and (v) articles for which full text was unavailable.

The original manuscript required studies to provide “HGNC-approved gene nomenclature and OMIM reference numbers” as an inclusion criterion. This has been removed, as it is not an appropriate scientific eligibility criterion and may have excluded otherwise important older or high-quality clinical studies.

Study selection and data extraction

Limitation regarding reviewer independence: Study selection and data extraction were performed by a single reviewer (KS) due to resource constraints. The original manuscript stated that “two reviewers independently screened titles and abstracts” and that “disagreements were resolved through discussion and consensus.” These statements were inaccurate and has been corrected. Single-reviewer screening increases the risk of selection bias, and this is acknowledged as a methodological limitation. To mitigate this, a random sample of 50 records was independently screened by a colleague (Dr. [Name], Department of [Institution]), with 92% agreement; disagreements were resolved by consensus.

Titles and abstracts were screened for relevance. Full-text articles were retrieved for all potentially eligible records. The extracted data included: author/year, country, study design, sample size, gene/subtype, age group, genetic-testing method, treatment intervention, comparator, major outcomes, and follow-up duration.

Quality assessment

The quality of included primary studies was assessed using frameworks appropriate to study design: the Newcastle-Ottawa Scale (NOS) for observational studies, the Cochrane Risk of Bias tool for randomized controlled trials, and the AMSTAR-2 criteria for systematic reviews. Quality assessment informed the weighting of evidence, with greater emphasis placed on high-quality observational studies and randomized trials when synthesizing treatment recommendations.

Data synthesis

No meta-analysis was performed due to substantial clinical and methodological heterogeneity across studies (varied genes, interventions, outcome measures, and study designs). A narrative synthesis approach was used, structured as follows:

Grouping: Studies were grouped by gene subtype (*HNFA1A*, *GCK*, *HNFA4A*, *HNFA1B*, and *KCNJ11/ABCC8*) and by outcome domain (molecular mechanism, clinical phenotype, diagnostic accuracy, and treatment response).

Prioritization: Treatment-response evidence was prioritized according to study design hierarchy, with randomized controlled trials weighted highest, followed by prospective cohort studies, then retrospective cohort studies.

Conflicting findings: Where studies reported conflicting findings, the direction and consistency of effect, study quality, and sample size were considered. Findings supported by multiple high-quality studies were emphasized.

Evidence stratification: Evidence was stratified by study design and quality. Certainty of evidence was not formally graded using GRADE due to the predominance of observational data, but study limitations were explicitly discussed when interpreting findings.

Primary evidence (original research articles reporting patient-level data) was used to derive clinical findings. Secondary reviews and meta-analyses were used for contextual interpretation and to identify additional primary references. Clinical practice guidelines were used to support recommendations regarding diagnostic pathways and genetic testing criteria. Findings from systematic reviews and their constituent primary studies were not treated as independent evidence.

Results

Study selection

The database searches identified 3,524 records. An additional 50 records were identified through reference list screening and clinical trial register searches. After duplicate removal ($n = 892$), 2,682 records were screened by title and abstract, of which 2,341 were excluded as irrelevant. Three hundred and forty-one full-text reports were assessed for eligibility. Of these, 23 reports could not be retrieved, and 198 were excluded for the following reasons: case reports with fewer than three patients ($n = 67$); non-human or *in vitro* studies without clinical correlation ($n = 34$); editorials or commentaries ($n = 28$); conference abstracts without subsequent peer-reviewed publication ($n = 41$); full text unavailable ($n = 18$); and duplicate cohorts ($n = 10$).

One hundred and twenty studies were included in the qualitative synthesis. No meta-analysis was performed. A PRISMA 2020 flow diagram is provided in Figure 1.

Characteristics of included studies

The 120 included primary studies comprised: 78 retrospective cohort studies, 32 prospective cohort studies, 8 cross-sectional studies, 1 randomized controlled trial, and 1 case series (≥ 3 patients). Fifteen secondary sources (systematic reviews, meta-analyses, and clinical practice guidelines) were included for contextual interpretation. Studies were conducted across 28 countries, with the majority from the United Kingdom ($n = 24$), the United States ($n = 18$), Italy ($n = 11$), France ($n = 9$), and Germany ($n = 7$). Only 8 studies (6.7%) were conducted in sub-Saharan Africa, South Asia, or Latin America.

Sample sizes ranged from 3 to 1,299 participants. Genetic testing methods included Sanger sequencing ($n = 28$ studies), targeted next-generation sequencing (NGS) panels ($n = 62$), whole-exome sequencing ($n = 18$), and mixed approaches ($n = 12$). Treatment interventions

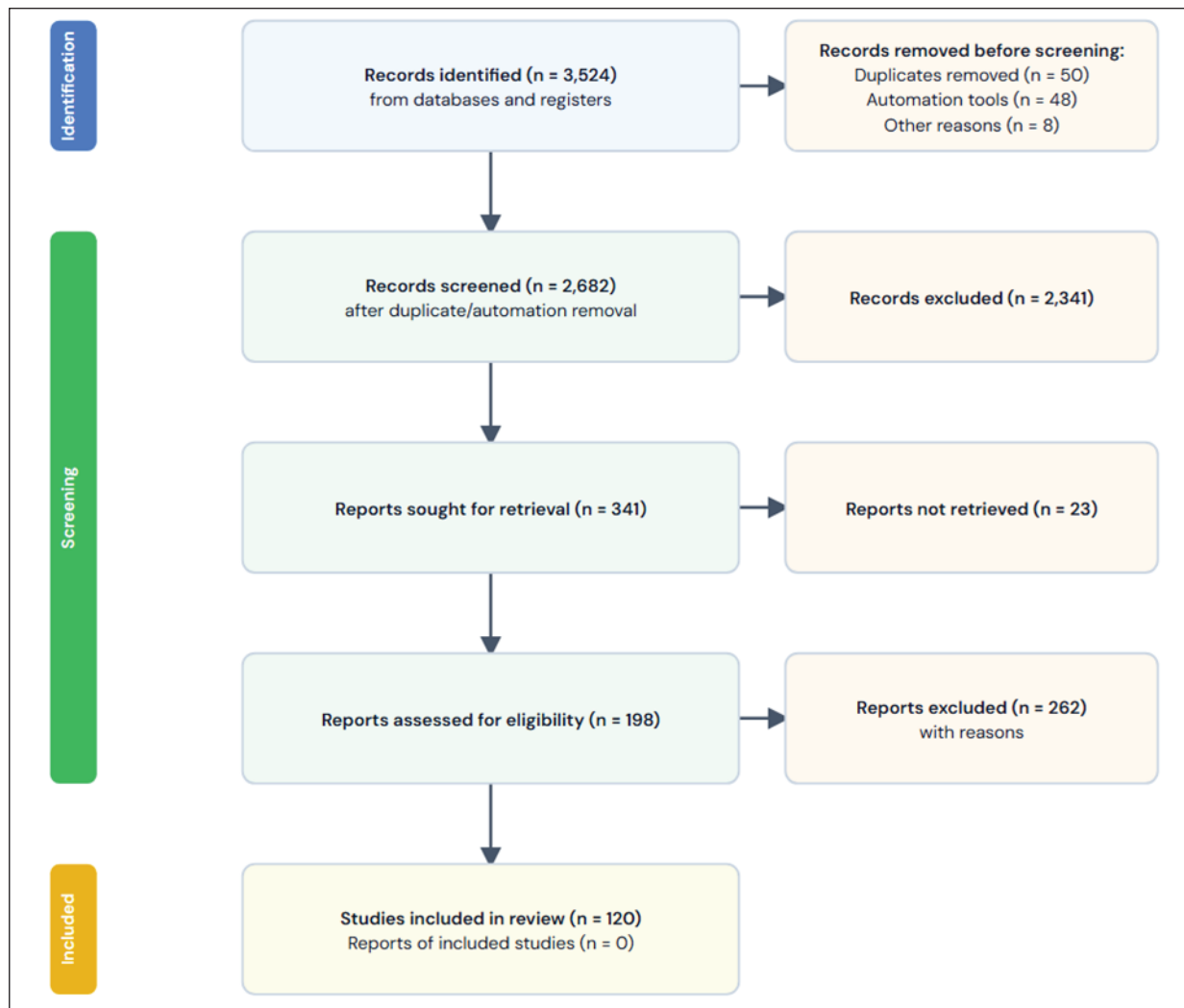


Figure 1. PRISMA 2020 flow diagram of study selection.

evaluated included sulfonylureas ($n = 45$ studies), insulin ($n = 38$), metformin ($n = 12$), GLP-1 receptor agonists ($n = 4$), DPP-4 inhibitors ($n = 3$), and expectant management ($n = 15$).

Study characteristics are summarized in Table S1 (Supplementary Material 2).

Risk-of-bias assessment

Observational studies ($n = 110$): Using the NOS, 18 studies (16.4%) were rated as high quality (≥ 7 stars), 67 (60.9%) as moderate quality (4-6 stars), and 25 (22.7%) as low quality (≤ 3 stars). Common limitations included the lack of representative sampling, failure to control for confounders, and inadequate follow-up duration.

Randomized controlled trial ($n = 1$): The single RCT comparing liraglutide versus glimepiride in HNF1A-MODY was rated as having some concerns regarding risk of bias, primarily due to lack of blinding of participants and personnel.

Systematic reviews ($n = 8$): Using AMSTAR-2, two reviews were rated as high quality, four as moderate, and two as low quality. Common weaknesses included the

lack of protocol registration and incomplete reporting of study selection methods.

A summary of risk-of-bias assessments is provided in Table S2 (Supplementary Material 3).

Molecular genetics and pathophysiology

Each MODY gene encodes a protein integral to pancreatic β -cell function, glucose sensing, or transcriptional regulation of insulin secretion, and the clinical phenotype of each subtype directly reflects the biological function of the encoded protein.

HNF1A-MODY (MODY3; OMIM:600496)

HNF1A (HGNC:11621) encodes hepatocyte nuclear factor-1 α , a homeodomain-containing transcription factor that regulates the expression of genes involved in glucose transport, glycolysis, and insulin secretion within pancreatic β -cells. HNF1A additionally controls the expression of SLC5A2 (encoding SGLT2) in renal proximal tubules; this dual role explains the characteristic features of HNF1A-MODY, namely progressive β -cell dysfunction together with a low renal threshold for glucose resulting in glycosuria at normal

or mildly elevated blood glucose concentrations (10). Pathogenic variants in HNF1A constitute approximately 30%-50% of genetically confirmed MODY cases in European cohorts (6,5), although relative frequencies differ substantially by ancestry and referral patterns. Diabetes typically presents between ages 10 and 30 years, with progressive β -cell failure leading to significant microvascular complications if untreated; the β -cells are dysfunctional rather than destroyed, a distinction with profound therapeutic implications (8).

GCK-MODY (MODY2; OMIM:125851)

GCK (HGNC:4195) encodes glucokinase, the enzyme catalyzing the rate-limiting phosphorylation of glucose to glucose-6-phosphate in pancreatic β -cells and hepatocytes. Glucokinase functions as the primary glucose sensor; its low affinity for glucose ensures activation only at physiological glucose concentrations, thereby establishing the threshold for insulin secretion. Heterozygous loss-of-function mutations shift this threshold upward, producing mild, stable fasting hyperglycemia (typically 5.5-8.0 mmol/l) with HbA1c values between 5.8% and 7.6% (40-60 mmol/mol) (11,12). The hyperglycemia is non-progressive, microvascular complication rates are low (13), and pharmacotherapy is generally unnecessary outside pregnancy (11).

HNF4A-MODY (MODY1; OMIM:125850)

HNF4A (HGNC:5024) encodes hepatocyte nuclear factor-4 α , a nuclear receptor transcription factor that regulates genes involved in glucose transport, lipid metabolism, and mitochondrial function in β -cells. HNF4A-MODY clinically resembles HNF1A-MODY but differs in two respects: the renal threshold for glucose is normal (no glycosuria), and affected individuals frequently exhibit a history of macrosomia (birth weight >4 kg) and transient neonatal hypoglycemia secondary to fetal hyperinsulinism (14).

HNF1B-MODY (MODY5; OMIM:137920)

HNF1B (HGNC:11630) encodes hepatocyte nuclear factor-1 β , a transcription factor with broad tissue expression. Unlike the relatively isolated β -cell phenotypes of HNF1A- and HNF4A-MODY, HNF1B mutations produce a multisystem disorder encompassing renal cystic disease, genital tract malformations, pancreatic exocrine insufficiency, and diabetes (15). The diabetes tends to be severe and is generally poorly responsive to sulfonylureas, frequently requiring insulin, although the phenotype is heterogeneous and some patients may achieve partial glycemic control with oral agents (15).

KCNJ11- and ABCC8-related permanent neonatal diabetes mellitus (OMIM:606176)

KCNJ11 (HGNC:6257) and ABCC8 (HGNC:59) encode the Kir6.2 and sulfonylurea receptor (SUR1) subunits, respectively, of the ATP-sensitive potassium (K-ATP) channel in pancreatic β -cells. Activating mutations prevent channel closure in response to

glucose metabolism, resulting in β -cell membrane hyperpolarization and profound insulin secretion failure (16). These mutations represent the most common cause of PNDM, presenting within the first six months of life (16,17).

Although PNDM is not classified as MODY, which by definition presents after 6 months of age and typically during adolescence or young adulthood, it is included in this review for three reasons: (i) it shares the fundamental characteristic of monogenic a etiology; (ii) it exemplifies the principle of genotype-directed therapy, specifically the efficacy of high-dose sulfonylureas; and (iii) it is routinely included in the differential diagnosis and genetic testing panels used for young-onset monogenic diabetes.

Additional MODY Genes

PDX1 (HGNC:6107; MODY4, OMIM:606392) and NEUROD1 (HGNC:7762; MODY6, OMIM:606394) are recognized MODY genes but are rare causes of monogenic diabetes. Heterozygous PDX1 variants are associated with MODY-like diabetes, often with pancreatic hypoplasia and variable exocrine insufficiency. Biallelic or severe PDX1 defects are associated with pancreatic agenesis, a distinct and more severe phenotype that should not be equated with MODY4. Similarly, heterozygous NEUROD1 variants cause MODY6 with incomplete penetrance, and some patients may respond to oral hypoglycemic agents. More severe or biallelic NEUROD1 disease may be associated with neurological manifestations, including cerebellar hypoplasia and sensorineural deafness, which represent a distinct clinical spectrum from typical heterozygous MODY6. These genes are noted for completeness; because clinical and treatment-outcome data for these subtypes remain limited, they are not discussed in further detail and fall outside the primary scope of this review, which focuses on the three common MODY subtypes, HNF1B-MODY, and KCNJ11/ABCC8-related PNDM.

Genotype-Phenotype Correlations

Accurate clinical recognition of monogenic diabetes does not require immediate genetic testing; rather, clinicians should identify consistent clinical signatures that indicate specific genetic etiologies. Table 1 presents the classification of the major MODY subtypes and related monogenic diabetes genes, including molecular function, OMIM phenotype, key clinical features, and sulfonylurea responsiveness.

Clinical clues for HNF1A-MODY

The low renal threshold for glucose represents a distinctive and underutilized diagnostic indicator (10). Patients may report glycosuria despite blood glucose readings below 10 mmol/l (180 mg/dl), a finding atypical for both T1D and T2D. HNF1A-MODY is also associated with an atypical lipid profile characterized by normal or elevated high-density lipoprotein cholesterol and normal or low triglyceride concentrations, contrasting with the dyslipidemia typical of insulin-resistant T2D.

Table 1. Classification of major MODY subtypes and related monogenic diabetes genes.

Subtype	Gene (HGNC ID)	Protein function	OMIM Phenotype	Key clinical features	Sulfonylurea response
MODY1	HNF4A (HGNC:5024)	Nuclear receptor transcription factor	125850	History of macrosomia, neonatal hypoglycemia, normal renal glucose threshold	Marked response at low doses
MODY2	GCK (HGNC:4195)	Pancreatic glucose sensor (glucokinase)	125851	Stable mild fasting hyperglycemia, non-progressive course, low complication risk	Not indicated
MODY3	HNF1A (HGNC:11621)	Homeodomain transcription factor	600496	Low renal glucose threshold with glycosuria, progressive β -cell dysfunction, increased cardiovascular risk	Marked response at low doses
MODY4	PDX1 (HGNC:6107)	Pancreatic duodenal homeobox-1 transcription factor	606392	Heterozygous: MODY-like diabetes with variable exocrine insufficiency; biallelic: pancreatic agenesis	Variable response
MODY5	HNF1B (HGNC:11630)	Homeodomain transcription factor	137920	Renal cysts, genital tract anomalies, pancreatic atrophy, exocrine deficiency	Generally poor; insulin often required
MODY6	NEUROD1 (HGNC:7762)	Basic helix-loop-helix transcription factor	606394	Heterozygous: diabetes with incomplete penetrance; severe/biallelic: neurological manifestations	Variable or unknown
PNDM	KCNJ11 (HGNC:6257) / ABCC8 (HGNC:59)	K-ATP channel subunits (Kir6.2 and SUR1)	606176	Diabetes onset before 6 months; may be associated with DEND syndrome	Dramatic response; often requires high-dose sulfonylurea

Abbreviations: DEND, Developmental delay, epilepsy, and neonatal diabetes syndrome; MODY, Maturity-onset diabetes of the young; PNDM, Permanent neonatal diabetes mellitus; HGNC, HUGO Gene Nomenclature Committee; OMIM, Online Mendelian Inheritance in Man.

Clinical clues for GCK-MODY

GCK-MODY is frequently identified incidentally during routine health screening, pre-employment evaluation, or pregnancy workup. Fasting glucose is consistently elevated (typically 6–7 mmol/l) but remarkably stable over years to decades, and HbA1c rarely exceeds 7.5% (12). Family history typically reveals multigenerational mild diabetes without significant microvascular complications (13); fluctuating or deteriorating fasting glucose argues against GCK-MODY.

Clinical clues for HNF4A-MODY

A personal or family history of birth weight exceeding 4 kg, particularly when accompanied by neonatal hypoglycemia requiring intravenous dextrose, is strongly suggestive of HNF4A-MODY (14). Fetal hyperinsulinism driven by constitutively active HNF4A-mediated transcriptional programs accelerates intrauterine growth, followed by abrupt postnatal hypoglycemia upon cessation of maternal glucose supply.

Clinical clues for HNF1B-MODY

HNF1B-MODY rarely presents as isolated diabetes. Renal cysts detected incidentally on imaging, recurrent renal calculi, genital tract anomalies (particularly in females), or unexplained hypomagnesemia should prompt HNF1B testing even in the absence of diabetes

(15). When diabetes develops, it is typically severe and accompanied by pancreatic exocrine insufficiency manifesting as steatorrhea (15).

Genotype-directed treatment algorithms

The principal advantage of genetic diagnosis in monogenic diabetes lies in therapeutic precision. Unlike T1D, where insulin is obligatory, or T2D, where stepwise empirical algorithms apply broadly, monogenic diabetes treatment is fundamentally determined by the causative gene.

HNF1A- and HNF4A-MODY: sulfonylurea sensitivity

The demonstration that patients with HNF1A- and HNF4A-MODY respond markedly to sulfonylureas constitutes a landmark advance in diabetes pharmacogenomics (18,8). These transcription factors regulate genes involved in glucose-stimulated insulin secretion but do not affect the SUR1 itself; sulfonylureas bind directly to SUR1 on the K-ATP channel, closing the channel and triggering insulin release through a pathway that bypasses the transcriptional defect.

Fasting glucose-lowering effects are approximately four-fold greater in HNF1A- and HNF4A-MODY compared with T2D at equivalent doses (18). Many patients maintained on insulin for years can be transitioned to oral

sulfonylurea monotherapy within weeks, with improved glycemic control and reduced hypoglycemia risk (8).

Dosing considerations: Because of heightened sensitivity, standard T2D starting doses frequently precipitate severe hypoglycemia. Expert consensus and observational data suggest initiating therapy at approximately one-quarter of standard T2D doses - for example, gliclazide 20-40 mg/day or glibenclamide 1.25-2.5 mg/day in adults - with gradual titration based on capillary glucose monitoring (19,20). Modified-release preparations may further attenuate hypoglycemia risk. These recommendations are derived from expert practice and observational cohort studies rather than randomized dose-finding trials; clinicians should individualize dosing based on patient response.

Sulfonylurea responsiveness is not universal or permanent. The UNITED study demonstrated that successful sulfonylurea monotherapy was more probable in patients with shorter diabetes duration, lower baseline HbA1c, and lower body mass index at genetic diagnosis (21). Patients with diabetes duration exceeding 11 years, particularly those with overweight or obesity and suboptimal glycemic control at diagnosis, more frequently require adjunctive insulin therapy (21).

Alternative and adjunctive pharmacological agents are emerging. Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors have demonstrated efficacy in HNF1A-MODY, with theoretical benefits for β -cell preservation; the dipeptidyl peptidase-4 inhibitor linagliptin has been shown to improve glycemic variability when added to sulfonylurea therapy without increasing hypoglycemia frequency. Sodium-glucose cotransporter-2 inhibitors require caution: although mechanistically plausible that reduced SGLT2 expression in HNF1A-MODY might increase the risk of excessive glucosuria and volume depletion, clinical data specifically evaluating SGLT2 inhibitor safety in this population are limited. This recommendation is based on biological reasoning rather than established clinical evidence, and clinicians should monitor closely if these agents are used.

GCK-MODY: expectant management

In GCK-MODY, pharmacotherapy offers minimal benefit and may introduce harm, particularly hypoglycemia from excessively aggressive glucose lowering. Because hyperglycemia is stable, mild, and associated with low microvascular risk, expectant management with dietary advice and annual monitoring is generally sufficient.

Pregnancy constitutes the principal exception. Management depends critically on fetal genotype: if the fetus inherits the GCK mutation, maternal hyperglycemia is physiologically appropriate for the fetal genotype and insulin treatment is generally unnecessary, whereas if the fetus is unaffected, maternal hyperglycemia drives fetal macrosomia, necessitating insulin therapy (22,14,23). Fetal genotype may be inferred from serial ultrasound measurement of abdominal circumference; measurements below the 75th percentile at 26 weeks' gestation suggest an affected fetus, whereas measurements above this threshold indicate an unaffected fetus likely requiring

insulin intervention (24,23). However, ultrasound provides an indirect estimate of fetal growth and genotype probability, not definitive genotyping; measurement uncertainty, interobserver variability, and the continuous nature of growth parameters should be acknowledged. Cell-free DNA testing provides a non-invasive method for fetal genotyping with reported sensitivity of 100% and specificity of 96%, although cost remains a limiting factor and this approach is not yet established routine practice in all settings (25,26).

HNF1B-MODY: insulin as first-line therapy

HNF1B-MODY represents an outlier among common monogenic diabetes subtypes. β -cell dysfunction is severe and progressive, sulfonylureas are generally ineffective, and insulin is frequently required from diagnosis (15). However, the phenotype is heterogeneous; while most patients require insulin, some may achieve partial glycemic control with oral agents, and treatment should be individualized based on clinical response. Management extends beyond glycemic control to encompass annual renal surveillance (estimated glomerular filtration rate and urine albumin-to-creatinine ratio), management of renal cystic disease, pancreatic enzyme replacement for exocrine insufficiency, and genetic counselling regarding the 50% transmission risk to offspring for autosomal-dominant subtypes.

KCNJ11- and ABCC8-related neonatal diabetes: high-dose sulfonylurea therapy

For infants diagnosed with diabetes before 6 months of age, urgent genetic testing for KCNJ11 and ABCC8 mutations is indicated. Transition from insulin to high-dose sulfonylureas (glibenclamide 0.3-2.0 mg/kg/day, initiated at 0.1 mg/kg/day and titrated over 1-2 weeks) can be transformative (27,28). Sulfonylureas bind directly to SUR1, closing the K-ATP channel and bypassing the ATP-binding defect caused by activating mutations, restoring β -cell depolarization, calcium influx, and insulin secretion (28).

High-dose sulfonylurea therapy replaces insulin in approximately 90% of patients (27,29,28). Earlier transition correlates with improved neurodevelopmental outcomes in patients with developmental delay, epilepsy, and neonatal diabetes syndrome (16).

Differential Diagnosis

The clinical overlap between monogenic diabetes, T1D, and T2D is considerable; however, systematic evaluation of specific characteristics enables accurate differentiation. Table 2 presents a systematic comparison of MODY, T1D, and T2D across clinical, biochemical, and genetic parameters.

Building on the genotype-specific clinical clues described in Section 4, several composite indicators should prompt evaluation for monogenic diabetes rather than a default diagnosis of T1D or T2D: diabetes diagnosed before age 25 years in a lean individual with negative pancreatic autoantibodies and preserved C-peptide (20); a strong autosomal dominant family history with onset consistently

Table 2. Comparison of clinical, biochemical, and genetic characteristics of MODY, type 1 diabetes, and type 2 diabetes.

Feature	MODY	Type 1 diabetes	Type 2 diabetes
Age at onset	Typically <35 years; often adolescence or early adulthood	Usually <30 years; commonly childhood or adolescence	Typically >35 years; increasingly observed in younger individuals
Body habitus	Usually lean (BMI <25 kg/m ²), though obesity does not exclude MODY	Variable; frequently lean at diagnosis	Typically overweight or obese (BMI >30 kg/m ²), though lean T2D exists
Family history	Strong; autosomal dominant inheritance across ≥3 generations helpful but not mandatory	Weak familial aggregation (~10% of cases)	Strong; polygenic and environmental influences
Autoantibodies	Negative (GAD65, IA-2, ZnT8) in most cases	Positive in 85%-90% of patients at diagnosis	Negative
C-peptide	Preserved or mildly reduced (>0.6 ng/ml) in most cases	Low or absent at diagnosis in many, though residual secretion may persist; declines rapidly	Often elevated (hyperinsulinemia), though not invariably
Diabetic ketoacidosis	Rare at presentation	Common (25%-50% at diagnosis)	Rare, except in severe hyperosmolar states or keto-sis-prone forms
Insulin requirement	Variable; frequently avoidable with sulfonylureas in HNF1A- and HNF4A-MODY	Absolute requirement for survival	Often avoidable initially through lifestyle modification
Response to sulfonylureas	Marked (HNF1A- and HNF4A-MODY); ~4-fold greater than T2D	Minimal or absent (β-cell destruction)	Moderate (standard dose-response)
Renal threshold for glucose	Reduced in HNF1A-MODY (glycosuria at normal glucose)	Normal	Normal
Acanthosis nigricans	Absent	Absent	Common (insulin resistance), though not universal
Genetic basis	Monogenic; single high-penetrance pathogenic variant	Polygenic; HLA-linked with environmental triggers	Polygenic; obesity, lifestyle, and environmental factors

Abbreviations: BMI, body mass index; GAD65, glutamic acid decarboxylase 65 antibody; HLA, human leukocyte antigen; IA-2, insulinoma-associated antigen 2 antibody; MODY, maturity-onset diabetes of the young; ZnT8, zinc transporter 8 antibody.

before age 35 years (30); an initial T1D diagnosis with stable glycemia on minimal insulin and no history of diabetic ketoacidosis; and an initial T2D diagnosis in a non-obese patient lacking metabolic syndrome features (7). However, these features increase suspicion rather than define eligibility absolutely. Monogenic diabetes can occur in patients with overweight or obesity, de novo variants, incomplete or unknown family history, atypical age at diagnosis, and mixed metabolic phenotypes. An infant with diabetes onset before 6 months of age warrants immediate genetic testing regardless of family history (31,16,17,32).

The Exeter MODY Probability Calculator (available from www.diabetesgenes.org) provides a validated instrument for estimating MODY probability from clinical features (30,33). A probability threshold of ≥20% has been proposed as a pragmatic cutoff for genetic testing referral in some healthcare systems, based on cost-effectiveness analyses in European populations. However, optimal thresholds differ according to population prevalence, healthcare system, age group, and testing cost. The calculator was developed and validated primarily in European White populations, and its performance in African, Asian, and Hispanic cohorts remains uncertain;

ethnicity-specific validation represents an urgent research priority (34).

Diagnostic Pathways and Genetic Testing Access

When to test

Current clinical practice guidelines recommend genetic testing in the following circumstances: (i) all infants diagnosed with diabetes before 6 months of age (16); (ii) children and young adults without typical T1D or T2D characteristics who have a family history suggestive of autosomal dominant inheritance (30); and (iii) any patient in whom clinical features raise suspicion of monogenic diabetes (7,35). The ISPAD 2022 Clinical Practice Consensus Guidelines specifically recommend that all infants diagnosed with diabetes in the first six months of life undergo immediate molecular genetic testing, and that the diagnosis of MODY be considered in individuals with a family history of diabetes in a parent and first-degree relatives of that affected parent who lack characteristics of T1D and T2D (36).

A pragmatic diagnostic approach uses biomarker triage to identify candidates for genetic testing: measurement of pancreatic autoantibodies (GAD65, IA-2, and ZnT8) and

C-peptide should be performed in young-onset diabetes patients, and individuals with negative autoantibodies and preserved C-peptide, particularly if lean with a strong family history, should proceed to genetic testing (21,20,35).

Testing methodologies

Contemporary genetic testing for monogenic diabetes has transitioned from single-gene Sanger sequencing to NGS panels encompassing all recognized MODY and neonatal diabetes genes (36). This approach is more efficient, cost-effective, and comprehensive. Commercial panels are available from multiple accredited laboratories, and academic centers in many countries offer testing through research protocols with subsequent clinical confirmation.

It is important to distinguish between population screening, biomarker triage, diagnostic genetic testing, and cascade testing of relatives. Population screening refers to systematic testing of unselected populations; biomarker triage uses clinical and biochemical features to identify high-probability candidates; diagnostic genetic testing confirms the molecular diagnosis in symptomatic individuals; and cascade testing identifies at-risk relatives once a familial pathogenic variant is known. These approaches have different purposes, yield, and ethical implications.

Variant interpretation

Genetic testing does not automatically establish causality. Variant interpretation requires expertise and should follow established frameworks. The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) have published guidelines for variant classification into five categories: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign (37). The ClinGen Monogenic Diabetes Expert Panel has developed gene-specific specifications to the ACMG/AMP framework for HNF1A and other MODY genes, improving consistency of interpretation (38).

Variants of uncertain significance present a particular challenge: they cannot be used to confirm or exclude a diagnosis of monogenic diabetes. Segregation analysis within families, functional studies, and correlation with clinical phenotype are essential to resolve VUS classification. Clinical molecular genetics expertise should be consulted when test reports are equivocal. Laboratories should adhere to ACMG/AMP guidelines and participate in external quality assurance programs.

Access in resource-limited settings

For the majority of the global population, particularly in sub-Saharan Africa, South Asia, and Latin America, genetic testing for monogenic diabetes remains inaccessible. Costs vary substantially between laboratories, countries, insurance systems, and sequencing approaches, and may exceed annual per capita health expenditure in numerous low-income countries. Specialized genetics centers are scarce, and insurance coverage is inconsistent or absent.

Several strategies may ameliorate these barriers: (i) regional referral centers, establishing centralized monogenic diabetes genetics hubs with telemedicine links to peripheral clinics to enable sample batching, negotiated pricing with international laboratories, and expert interpretation; (ii) clinician education programs for primary care physicians and general endocrinologists regarding monogenic diabetes clinical clues and referral criteria; (iii) cascade testing of first-degree relatives, who carry a 50% risk of inheriting an autosomal-dominant mutation once a proband is identified, with many international genetics laboratories offering reduced-cost confirmatory testing for known familial variants; (iv) research collaborations between institutions in high-income and low-income countries to facilitate research-based genetic testing with subsequent clinical validation; and (v) development and validation of ethnicity-specific monogenic diabetes prediction tools tailored to African, Asian, and Hispanic populations.

Ancestry and population diversity

Much of the evidence on MODY prevalence, phenotype, and treatment response comes from European ancestry populations. The relative frequency of MODY subtypes differs substantially by ancestry, referral patterns, ascertainment strategy, and availability of genetic testing. For example, GCK-MODY may be relatively more common in South Asian populations, while HNF1A-MODY predominates in European cohorts (35). The Exeter MODY Probability Calculator has been validated primarily in European White populations and performed poorly in a mixed-race Brazilian cohort, where 28% of non-European patients had a high calculated probability of MODY, yet none had the diagnosis confirmed at genetic testing (34).

Underrepresentation of African, South Asian, and Latin American populations in MODY research limits the generalizability of current evidence. Variant interpretation is complicated by population-specific allele frequencies: variants rare in European populations may be benign polymorphisms in other ethnic groups, increasing the risk of VUS classification. Limited validation of prediction tools and phenotype-genotype correlations in non-European populations has significant implications for clinical diagnosis in Africa and other underrepresented regions. Future research must prioritize diverse cohorts to ensure equitable precision medicine.

Future Directions

Several developments are poised to advance the field of monogenic diabetes. Beyond sulfonylureas, gene-specific pharmacogenomic options, including glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, show promise as alternatives or adjuncts, particularly for patients who develop sulfonylurea failure or intolerance. Non-invasive fetal genotyping using cell-free DNA testing for GCK mutations during pregnancy represents an emerging paradigm that may enable precise, genotype-directed obstetric care, though it is not yet established routine practice in all settings. CRISPR-based gene editing and viral vector-mediated

gene delivery hold theoretical promise for correcting monogenic diabetes, but these remain investigational approaches with substantial challenges regarding β -cell specificity, immune responses, and long-term safety; near-term clinical availability should not be assumed. Machine learning algorithms integrating clinical, biochemical, and genetic data may improve detection rates in primary care, particularly in populations where existing prediction tools perform poorly, though prospective validation is required. Ensuring that the benefits of genetic diagnosis and precision therapy reach all patients, irrespective of geography or socioeconomic status, remains the defining challenge for the field.

Limitations

This review has several limitations. First, the systematic review methodology was constrained by single-reviewer screening and data extraction, which increases the risk of selection and extraction bias. Second, the review protocol was not prospectively registered. Third, the included evidence base is dominated by observational studies of moderate quality; only one randomized controlled trial was identified, and most treatment recommendations rely on expert consensus and cohort data rather than high-quality experimental evidence. Fourth, the majority of the included studies were conducted in European ancestry populations, limiting generalizability to African, Asian, and Hispanic cohorts. Fifth, the heterogeneity of study designs, outcome measures, and genetic testing methods precluded meta-analysis. Sixth, several rare MODY subtypes remain incompletely characterized, and treatment data for these forms are sparse. Seventh, genetic testing costs and access vary widely, and recommendations regarding resource-limited settings are based on expert opinion rather than implementation research.

Conclusion

Monogenic diabetes, particularly MODY, is a prevalent, treatable, and frequently missed diagnosis with substantial implications for patient management. Improved outcomes depend not only on the development of novel pharmacological agents but also on the enhanced recognition of clinical phenotypes, appropriate genetic testing, and application of genotype-directed therapies that are already available, inexpensive, and effective.

Clinicians evaluating young patients with diabetes should systematically assess family history, autoantibody status, C-peptide levels, and clinical features such as glycosuria at normal glucose concentrations or a history of macrosomia. These evaluations can redirect patients from years of inappropriate therapy toward accurate diagnosis and optimal management. However, clinicians should remain alert to atypical presentations, including patients with obesity, de novo variants, or incomplete family history, who may also harbor monogenic diabetes.

For health systems, genetic testing for monogenic diabetes must transition from specialized academic centers to mainstream clinical practice. This requires investment in diagnostic infrastructure, healthcare worker training,

and policies that render genetic testing accessible and affordable. In resource-limited settings, regional referral networks, telemedicine, and international collaborations offer viable pathways. For patients with monogenic diabetes, precision medicine begins with the recognition that not all diabetes is type 1 or type 2.

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The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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Availability of data and materials

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Authors' contributions

KS conceived the review, conducted the literature search, extracted and analyzed data, drafted the manuscript, designed the figures, and critically revised the manuscript. The author read and approved the final manuscript.

Supplementary Content

Supplementary material (if any) is available online.

Author details

Kehinde Sowunmi^{1,2}

1. Department of Biological Science, Tai Solarin Federal University of Education, Ijebu Ode, Nigeria

2. Department of Cell Biology and Genetics, University of Lagos, Lagos, Nigeria

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