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Clinical Manifestations and Biomarkers of the Maturity-Onset Diabetes of the Young

REVIEW
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ABSTRACT

Maturity-onset diabetes of the young is the most common monogenic diabetes form affecting between 1% and 5% of all diabetes cases. Clinical characteristics include young onset (usually before 45 years), autosomal dominant inheritance, absence of autoantibodies and metabolic syndrome, and impaired glucose-dependent insulin secretion. To date, at least 14 maturity-onset diabetes of the young subtypes have been identified, harboring numerous mutations that contribute to highly heterogeneous clinical phenotypes. While much is known about the common subtypes of maturity-onset diabetes of the young linked to mutations in *HNF4A*, *GCK*, *HNF1A*, and *HNF1B*; little is known about relatively rare mutations in *IPF1/PDX1*, *NEUROD1*, *KLF11*, *PAX4*, *INS*, *BLK*, *ABCC8*, *KCNJ11*, and *APPL1* genes. However, with the advent of next-generation sequencing, rare maturity-onset diabetes of the young subtypes are being increasingly reported worldwide.

Although nearly 6 decades have passed since the first cases were identified, maturity-onset diabetes of the young is often misdiagnosed as type 1 or type 2 diabetes mellitus due to overlapping clinical features, limited use of genetic testing, and lack of awareness of this type of diabetes. Although there are many clinical characteristics suggesting the diagnosis of maturity-onset diabetes of the young, there is no single criterion. Identifying clinical features of different maturity-onset diabetes of the young subtypes can reduce the number and cost of genetic testing; On the other hand, early diagnosis will reduce the risks of inappropriate treatment and related side effects.

The aim of this review is to highlight the role of clinical features, demonstrate the effectiveness of clinical biomarkers in the differential diagnosis of maturity-onset diabetes of the young subtypes, and identify the most suitable candidates for genetic testing.

Keywords: Biomarkers, clinical manifestations, diabetes, diagnosis, maturity-onset diabetes of the young, MODY, monogenic diabetes, treatment

Introduction

According to the International Diabetes Federation, the worldwide population with diabetes is over half a billion in 2021 and is projected to reach 783 million by 2045.[1] The current classification of diabetes includes the common forms such as type 1, type 2, and gestational diabetes and less common forms such as pancreatogenic, drug/chemical-induced, infection- and endocrinopathy-induced, and monogenic diabetes.[2] Advances in molecular genetics have enabled the recognition of some commonalities between different types of diabetes as well as genetic traits that lead to different pathophysiological consequences in the same type of diabetes.[3]

Monogenic diabetes is a highly heterogeneous group comprising diabetes cases associated with certain genetic syndromes (Down, Klinefelter, Turner, and Wolfram syndromes) and non-syndromic disorders. Maternally inherited mitochondrial and neonatal (transient and permanent) diabetes and maturity-onset diabetes in the young (MODY) are considered non-syndromic forms.[2]

Maturity-onset diabetes of the young is the most common monogenic beta-cell disorder that can be distinguished from others by its younger age at onset (usually before age 45 years), multigenerational inheritance, and preserved endogenous insulin reserve. Autosomal dominant inheritance affects at least 3 successive generations.[4-6] The prevalence of MODY ranges from 1% to 5% among all diabetic patients, depending on the population.[5-7] Maturity-onset diabetes of the young differs from type 1 diabetes with the absence of autoimmune markers and from type 2 diabetes with lack of insulin resistance. Nevertheless, MODY cases can be frequently misdiagnosed as type 1 or type 2 diabetes.[8,9] There is a strong demand for definitive

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diagnosis with robust clinical biomarkers and low-cost rapid genetic tests.[3,10] This will facilitate clinical decision-making and extend precision treatment to all MODY patients.

In this review, the historical evolution of MODY will be summarized first. Subsequently, the general clinical features of MODY and the proposed new classification, the effectiveness of various biomarkers in the diagnosis, the diagnostic algorithm, treatment approach, and complications will be explained. Finally, the characteristics of MODY subtypes will be presented.

Historical Evolution

During the First International Congress of Endocrinology in Copenhagen in 1960, Fajans and Conn[11] reported mild, asymptomatic, non-obese diabetes cases seen in children, adolescents, or young adults from the USA. All were first-degree relatives of known diabetes patients. Diabetes was detected with oral glucose tolerance test (OGTT), and the blood glucose levels were improved with sulfonylureas. At the Fifth International Congress of Diabetes in Toronto in 1964, Fajans and Conn[12] used the term "maturity-onset type diabetes of childhood or of the young" for this type of diabetes. They emphasized on the mild course of diabetes and strong familial transmission. In 1974, Tattersall[13] reported a similar "mild diabetes form" showing a dominant inheritance pattern in 3 families for the first time in Europe. He was able to discontinue insulin in most of the patients, and he noticed that complications were less common than expected. However, in longer follow-up, typical severe microvascular and neuropathic complications developed in these cases.[14] At the time, clinicians were aware of only 2 types of diabetes: juvenile-onset diabetes (now type 1 diabetes) and maturity-onset diabetes (now type 2 diabetes).[14] While the first was characterized by severe hyperglycemia and rapid insulin requirement, primarily seen in children, adolescents, or young adults, the second was considered a mild diabetes form, which is often encountered in middle-aged or elderly people and can be controlled with diet and oral antidiabetic drugs (OADs).

Tattersall and Fajans,[14] meanwhile, proposed the abbreviation "MODY" for this type of diabetes; afterward, this term was adopted by the diabetes experts community. In fact, long before them, in 1928, Cammidge[15] was the first physician who reported the mild familial diabetes, with a dominant inheritance. However, he could not measure blood glucose, and the diagnosis of diabetes was solely based on glycosuria.

The molecular genetic etiology of MODY was first identified in the early 1990s by glucokinase mutation (GCK-MODY; MODY2)[16] followed by *hepatocyte nuclear factor-4 alpha* (*HNF4A*)-MODY (MODY1)[17], and *HNF1A*-MODY (MODY3).[18] Since then, at least 14 genes causing diabetes with MODY-like clinical features have been reported and are numbered MODY1 to MODY14.[19] Therefore, the researchers proposed a new nomenclature to nominate the MODY forms with the corresponding gene name (i.e., *HNF4A*-MODY, GCK-MODY, and *HNF1A*-MODY instead of MODY1, MODY2, and MODY3).[4] In accordance with the universal rules, in this review, care will be taken using the same nomenclature for MODY subtypes and italicize the abbreviated names of the relevant genes.

Etiology

Mutated MODY genes may impair insulin secretion due to developmental defects in pancreatic islet cells. Maturity-onset diabetes of the young is usually autosomal dominantly inherited, and patients often have a heterozygous mutation.[4,5,9,20] Autosomal recessive forms are less common, and they are usually responsible for neonatal diabetes. Maturity-onset diabetes of the young subtypes show a wide range of heterogeneity in terms of both genetic features and clinical manifestations.[21] Maturity-onset diabetes of the young genes can cause alterations in insulin secretion by impairing glucose metabolism, insulin sensing, or activation of adenosine triphosphate-sensitive potassium (*K-ATP*) channels on the beta-cell membrane.[22]

While much is known about classic MODY subtypes which were associated with mutations in *HNF4A*, *GCK*, *HNF1A*, and *HNF1B* genes, little is known about relatively rarer MODY subtypes due to mutations in *insulin promoter factor 1/pancreatic duodenal homeobox 1 (IPF1/PDX1)*, *NEUROD1*, *KLF11*, *CEL, PAX4*, *INS*, *BLK*, *ABCC8*, *KCNJ11*, and *APPL1* genes.[23] However, with the invention of next-generation sequencing (NGS), rare MODY subtypes (i.e., *IPF1/PDX1*-, *INS*-, and *ABCC8*-MODY) have been increasingly reported.[9,20,24] Notably, other subtypes such as *KLF11*-, *CEL*-, *KCNJ11*-, and *APPL1*-MODY are much rarer forms.[25] Mutations in maturity-onset diabetes of the young have also been related with other syndromes such as maternally inherited diabetes and Wolfram [also known as DIDMOAD) syndrome,[26] characterized with diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.[23]

Epidemiology

The estimated prevalence of MODY is less than 5%.[3,7,25] In the autoantibody-negative pediatric diabetes population, the prevalence is up to 6.5%.[20,24] The prevalence shows a wide range based on the populations studied as well as the criteria used to detect cases. The diagnosis of MODY is made between the ages of 1 and 44 years. [4-6] Therefore, up to 80% of cases are misdiagnosed as having type 1 or type 2 diabetes.[23,27] In the SEARCH for Diabetes in Youth (SEARCH) study of US children and adolescents with diabetes onset under 20 years of age, genetic screening confirmed that 8% of participants actually had MODY.[28]

While MODY has been described predominantly in Caucasian populations, it has been reported in almost all races (i.e., Asian Indian,

MAIN POINTS

- Classically, maturity-onset diabetes of the young (MODY) is considered as an early-onset, non-obese, and relatively mild form of diabetes occurring in at least 3 consecutive generations. However, only 50% of MODY cases today fit this description.
- Up to 80% of MODY cases are misdiagnosed as type 1 diabetes or type 2 diabetes. Increasing awareness of MODY among healthcare professionals will increase accurate diagnoses.
- Most of our epidemiological knowledge of MODY is based on studies investigating subtypes such as *GCK-, HNF4A, HNF1A-*, and *HNF1B*-MODY that are relatively common in Western societies. However, studies in other populations suggest that other MODY subtypes may be more common than expected.
- Improving the discriminative performance of clinical biomarkers will help reduce the number of patients referred for genetic testing and the cost of testing as well.
- The development and widespread use of low-cost genetic testing is necessary to facilitate the early recognition of MODY subtypes and to promote the dissemination of precision medicine.

Japan, Chinese, and Turkish).[26] Previous studies have shown that *HNF4A*-, *GCK*-, and *HNF1A*-MODY represent the most common MODY forms in the Western populations, accounting for 80%-90% of all MODY cases reported from the UK,[27] Europe,[29,30] and the USA.[28] Nevertheless, mutations in these genes account for 10%-20% of MODY cases in Asia (Japan, Korea, and China).[31] This means that up to 80% of Asian patients with MODY may remain genetically unidentified. Next-generation sequencing studies have shown that rarer forms of MODY, particularly *CEL-, BLK-, KLF11-, NEUROD1-*, and *ABCC8*-MODY, are more common than expected in some populations (e.g., Türkiye).[9,20] Double- and even triple-gene mutations have been reported, especially in populations where consanguineous marriages are more common.[20,25] The abundance of clinical features in such cases is notable.[20]

Old and Current Diagnostic Criteria

The definitive diagnosis of MODY necessitates genetic testing. However, in order to detect cases with clinical suspicion, the anamnesis should be well questioned, and a detailed physical examination including all systems should be performed. Clinical criteria for the diagnosis of MODY were proposed in the 1970s, based on the first families identified; The criteria included multigenerational, young-onset (age of onset less than 25 years) and non-insulin-required diabetes proven with preserved beta-cell reserve.[14] The first identified cases were thin, and none of them had diabetes presented with diabetic ketoacidosis (DKA). Despite that, today, only 50% of suspected cases referred for diagnosis of MODY have these classic features of the disease.[28] With the spread of genetic analyses such as NGS, more MODY cases have been detected over the age of 25 years. Maturity-onset diabetes of the young cases without parental history has been reported.[4-6]

Obesity helps to distinguish patients with MODY from those with type 2 diabetes.[9,10,32] Nevertheless, obesity has been reported in patients with rare forms of MODY, including *IPF1/PDX1-*, *NEUROD1-*,[32] *BLK-*,[13,21] *ABCC8-*,[33] *KLF11-*,[31] *PAX4-*,[31] and GCK-MODY[28] and even in more common MODY subtypes (i.e., *HNF1A-/HNF4A*-MODY).[34,35] A longitudinal study of obese or overweight children with diabetes in the USA, 'Treatment Options for Type 2 Diabetes in Adolescents and Youth' (TODAY trial) (TODAY trial) showed that 4.5% of patients actually had *HNF1A-*, *HNF4A-*, *GCK-*, *INS-*, or *KLF11*-MODY).[36] Therefore, obesity and overweight may be more common than previously believed at least in certain MODY subtypes.

As noted, having a body mass index (BMI) over 30 kg/m^2 or signs of insulin resistance (i.e., acanthosis nigricans), presentation with DKA, or even no family history of diabetes may not rule out a diagnosis of MODY.[25] The fact should be addressed when updating the existing guidelines for the screening of MODY. Current diagnostic criteria used for clinical suspicion of MODY are listed in Box 1.

Suggested New Classification of Maturity-Onset Diabetes of the Young

Within the scope of this review, the available literature on the clinical features, treatment, and complications of the globally reported MODY subtypes has been evaluated. Unknown variants, which have been increasingly reported in recent years, have caused some difficulties in understanding the pathogenesis and clinical significance of MODY subtypes. Therefore, the necessity of reclassification of MODY is being debated.

Box 1. Diagnostic Criteria for Clinical Suspicion of MODY

- Early-onset diabetes (between 1 and 44 years)
- Family history of diabetes in at least 3 consecutive generations
- Negative islet autoantibodies (GADA, IA2-A, IAA, and ZnT8A)
- Exclusion of type 1 and type 2 diabetes or metabolic syndrome
- Moderate fasting hyperglycemia (130-250 mg/dL or 7-14 mM/L)
- Measurable C-peptide levels during hyperglycemia after at least 3 years of diabetes-onset
- No insulin requirement or persistently low insulin requirement (e.g., <0.5 IU/kg/day) at onset
- No DKA even without insulin administration at onset
- BMI ≤25 kg/m^2
- Presence of additional clinical findings specific to MODY subtypes (e.g., presence of cystic kidney disease in the index patient or close relatives; low levels of hs-CRP)

BMI, body mass index; DKA, diabetic ketoacidosis; GADA, glutamic acid decarboxylase-65 antibody; hs-CRP, high-sensitivity C-reactive protein; IAA, insulin autoantibody; IA2-A, islet antigen-2 antibody; MODY, maturity-onset diabetes of the young; ZnT8A, zinc transporter 8.

In some of the MODY subtypes identified so far, very few patients with limited clinical features have been described. Based on clinical and genetic findings collected over the last 2 decades, MODY subtypes have been proposed to be reclassified under 3 categories as follows:[7,23]

1. Common MODY subtypes (i.e., *HNF4A-*, *HNF1A-*, *GCK-*, *HNF1B-*, *INS-*, *ABCC8-*, and *KCNJ11*-MODY);
2. Rare MODY subtypes, although identified in several families, there is sufficient genetic findings to classify them MODY (i.e., *IPF1/PDX1-*, *NEUROD1-*, and CEL-MODY or mutations in *RFX6* and *WSF1*); and
3. Genes reported as causative for MODY but without strong clues (i.e., *PAX4-*, *BLK-*, *APPL1-*, and *KLF11*-MODY, or mutation in *NKX6-1*).

Clinical Picture

The clinical picture in *HNF4A*-MODY is similar to *HNF1A*-MODY.[24,25] Fasting plasma glucose in GCK-MODY is usually between 100 and 140 mg/dL (5.6 and 7.8 mmol/L). Glycated hemoglobin A1c (HbA1c) typically stay within certain limits. Glycated hemoglobin A1c at onset is usually less than 7.5% (59 mmol/mol) if the patient is younger than 40 years; in contrast, HbA1c may be slightly higher if the patient is older.[8,16,24] Birth weight, if known, can provide useful information. Some women with *HNF4A*-MODY may have large-for-gestational-age babies with transient neonatal hyperinsulinemic hypoglycemia.[34] Similarly, a transient neonatal hypoglycemia may be observed in rare *HNF1A*-MODY cases.[35] Intrauterine growth retardation, urogenital system defects, and pancreatic hypoplasia are frequently encountered malformations in *HNF1B*-MODY.[37] Patients with GCK-MODY may have mild fasting hyperglycemia from birth.[24] The absence of DKA is useful in differentiating MODY from type 1 diabetes.[24,25,38] However, DKA may be rarely observed in patients with *HNF1A-*,[39] *HNF4A-*,[38] *PDX1-*,[25] *NEUROD1-*,[40] *PAX4-*,[10] and INS-MODY.[41]

No diabetes complications were reported in the first MODY families.[14] Later, as experience with MODY subtypes increased, it became clear that renal and retinal complications develop in *HNF4A*-, *HNF1A*-, *HNF1B*-, and *NEUROD1*-MODY subtypes to a comparable extent to type 1 and type 2 diabetes.[25,40,42] In fact, this is true for most of MODY subtypes, except for GCK-MODY, which has the best prognosis.[8,25,28,40] Cardiovascular disease (CVD) mortality in family members with *HNF1A*-MODY was higher than that in unaffected family members.[4] Nonetheless, complications in rare MODY subtypes are less well documented.[25] Longitudinal studies are required to follow rare MODY cases to progress to a complete picture. Since developing complications will require sufficient time, longitudinal studies are needed to follow up of rare cases.

Biomarkers

Previously, genetic testing was labor intensive and expensive and could not be done everywhere. Consequently, clinicians attempted to define some biomarkers to point out certain MODY subtypes. Biomarkers help to develop clinical guidelines, improve diagnosis, and finally reduce the number of patients referred to genetic testing. The most commonly used biomarkers to clinically distinguish certain MODY subtypes from classic type 1 and type 2 diabetes are C-peptide, high-sensitivity C-reactive protein (hs-CRP), cystatin-C, apolipoprotein M (ApoM), 1,5-anhydroglucitol (1,5-AG), transthyretin (TTR), complement 5 (C5), and complement 8 (C8), D-glycan, islet autoantibodies, high-density lipoprotein cholesterol (HDL-C), triglycerides, and sensitivity to sulfonylureas.[4,6-8,10,38,42-45] The rational, distinctive features and limitations of these biomarkers are shown in Table 1. Those markers that are relatively reliable will be discussed here.

C-peptide: According to the European Genetic Quality Network (EMQN), the diagnosis of MODY requires the preservation of beta cell function, with no need for exogenous insulin even a few years after the onset of the disease.[42] Adequate beta-cell function is evidenced by serum C-peptide levels greater than 0.6 ng/mL (200 pmol/L) and while blood glucose above 75 mg/dL (4.2 mmol/L). Urinary C peptide to creatinine ratio has been proposed as a more reliable biomarker to differentiate *HNF4A*- and *HNF1A*-MODY from established type 1 diabetes.[10]

Islet autoantibodies: Evaluation of patients with MODY should begin with the exclusion of type 1 diabetes. Negative islet autoantibodies [glutamic acid decarboxylase-65 (GADA), islet antigen 2 (IA2-A), endogenous insulin, and zinc transporter 8) exclude type 1 diabetes.[6,38] In adult patients, one should prefer GADA plus any 2 autoantibodies. Nevertheless, few case reports have been published showing positive IA2-A, albeit at low titer, in rare MODY subtypes.[24,38]

High-sensitivity C-reactive protein: In *HNF1A*-MODY, hs-CRP levels are typically lower than in other diabetes forms, thus making it a potential biomarker. Generally, hs-CRP levels lower than 0.75 mg/L can help differentiate *HNF1A*-MODY from other types of diabetes including MODY subtypes.[7,43]

Maturity-Onset Diabetes of the Young Risk Calculator

With the inclusion of clinical features and biomarkers, several MODY probabilistic tools have been developed. Among these, the MODY Risk Calculator was modeled by the University of Exeter for Caucasians aged 1-35 years and validated for the 3 classic MODY subtypes (*HNF4A*-, *GCK*-, and *HNF1A*-MODY).[46] The model includes current age, age at diabetes onset, gender, ethnicity, BMI, HbA1c, treatment regimen, parental diabetes, and specific health issues associated with certain MODY phenotypes. The case should be referred for genetic testing with a positive predictive value (PPV) of >10% if treated with insulin within 6 months of diabetes onset or with a PPV of >25% if not treated with insulin within 6 months of diagnosis (Box 2).

When to Order Genetic Test?

Genetic test should be ordered in cases if there is a high suspicion that the patient may not have type 1 or type 2 diabetes. Genetic testing indications should include:[22,24,47]

1. Young age at onset (1-44 years);
2. Strong family history of diabetes affecting at least 3 consecutive generation;
3. Features inconsistent with type 1 or type 2 diabetes such as low renal glucose threshold, too large or too small increase in plasma glucose on OGTT, low hs-CRP levels, low HDL-C levels, and higher insulin sensitivity;
4. Being low or normal weight (BMI less than 25.0 kg/m^2);
5. No DKA at onset;
6. No insulin requirement for at least 3 years of diabetes onset; and
7. Clinical features compatible with a specific MODY subtype (e.g., kidney anomalies in *HNF1B*-MODY).

The diagnostic algorithm for patients with suspected MODY is depicted in Figure 1.[4,5,7,8,47,48] Molecular genetic analysis aids to determine which mutation is responsible for the clinical picture. The type of test to be performed is dependent on the clinician's opinion. Obtaining information about previous genetic tests in the family can be very helpful.[24] A single-gene test may be ordered if the patient has features of a particular MODY subtype such as extra-pancreatic or renal involvement. Conversely, if the phenotype cannot be distinguished from other MODY forms, a multi-gene panel containing all MODY genes can be used. Finally, if the patient has relevant clinical manifestations but no mutation was identified with conventional genetic tests, more comprehensive genomic analysis may be considered.[7,22] Genetic counseling should be provided for the relatives of MODY patients.

Treatment

The optimal treatment of MODY differs depending on the mutated gene. Therefore, knowing the pathogenic variant is crucial in terms of the treatment decision and the prognosis of patients.

Glucokinase-maturity-onset diabetes of the young patients have a mild or moderate fasting hyperglycemia rather than postprandial hyperglycemia because these patients have adequate insulin secretion in response to glucose increase. Blood glucose can be controlled by lifestyle modifications (diet and physical activity) alone; except for pregnant women, these patients generally do not need pharmacological treatment of hyperglycemia.[5,47]

Nevertheless, the management of hyperglycemia in GCK-MODY during pregnancy should be taken more seriously. The decision of whether to treat with insulin depends on whether the mother, fetus, or even father carries the pathogenic *GCK* variant. According to this, (1) if the mother carries a pathogenic *GCK* variant, but the fetus does not, the risk of macrosomia increases as maternal hyperglycemia will cause fetal hyperinsulinemia; (2) conversely, if the mother and fetus carry the same pathogenic *GCK* variant, as the glucose threshold to induce insulin secretion will be similar in both, fetal insulin levels and

Table 1. Biomarkers Studied for Common MODY Subtypes and Their Limitations in Clinical Use

Biomarker	Rationale	Comments	Limitations
High C-peptide levels[4,6-8,10,38,42-45]	Marker for endogenous insulin secretion	UCPCR and fasting serum C-peptide levels can distinguish patients with MODY from patients with type 1 diabetes	The rate of C-peptide decline is highly variable between patients with type 1 diabetes
	Majority of type 1 diabetes patients become severely insulin deficient and C-peptide decreases to critical levels within 2-3 years of diagnosis; C-peptide levels persist in MODY	A UCPCR ≥0.2 nmol/mmol suggests that a genetic test may be appropriate	Even 5 years after diagnosis of type 1 diabetes, some patients may have detectable C-peptide levels
Low hs-CRP levels[4,6-8,10,43]	*HNF1A*-binding sites in the *CRP* gene promoter	Low serum hs-CRP levels in patients with *HNF1A*-MODY	Elevated hs-CRP levels during intercurrent infections
			Reduction in hs-CRP with the use of certain drugs such as aspirin, statins, and beta-blockers
			Inter- or intra-laboratory assay variability
			The accuracy for differentiating *HNF1A*-MODY from type 2 diabetes is 80%, while its accuracy is 75% when compared with other diabetes types
Low cystatin-C levels[8]	Cystatin-C is a marker of GFR	Except for *HNF1B*-MODY, there are no differences of cystatin-C levels between *HNF1A*-MODY and other diabetes subgroups	Differences between cystatin-C assays
	Cystatin-C levels are affected by CRP, whose concentration is decreased in *HNF1A*-MODY		The hypothesis that cystatin-C levels are altered by *HNF1A* mutations has not been confirmed
Low ApoM levels [8,10,44]	The promoter region of *ApoM* includes a binding site for *HNF1A*	ApoM concentrations are not different in patients with *HNF1A*-MODY and type 2 diabetes	Differences in methodology require standardization
	ApoM is potently transacted by *HNF1A in vitro*	ApoM levels are lower in *HNF1A*-MODY patients than in those with type 1 diabetes	Limited availability of ApoM testing Insufficient diagnostic accuracy in MODY
	Decreased *HNF1A* activity in humans leads to low plasma ApoM levels		
Low 1,5-AG levels[8]	*HNF1A* mutations are characterized by a low renal glucose threshold due to decreased expression of high-affinity low-capacity SGLT2	Plasma concentrations of 1,5-AG are lower in *HNF1A*-MODY compared to other types of diabetes with a similar HbA1c	Limited usefulness in pregnant women and patients with ESKD
			1,5-AG is not a specific biomarker for patients with HbA1c >9.0% (75 mmol/mol)
	A low renal threshold for glucose results in lower serum 1,5-AG levels		More research is needed in larger patient groups and other diabetes subgroups
Low TTR levels (Ref. 8)	Transcription of genes encoding *TTR* is regulated by *HNF1A* and *HNF4A*	Except for *HNF1A*-MODY, patients with *HNF4A*-MODY have lower TTR compared with other types of diabetes	The effects of mutations on TTR are too weak to be detected by measuring serum TTR concentrations
Low C5 and C8 levels[8]	Transcription of the *C5* and *C8* genes is regulated by the *HNF1A* and *HNF4A* transcription factors	*HNF4A*-MODY and *HNF1A*-MODY patients have reduced C5 and C8 levels compared with type 2 diabetes patients	Inflammatory states are linked with increased expression of complement factors

(*Continued*)

Table 1. Biomarkers Studied for Common MODY Subtypes and Their Limitations in Clinical Use (*Continued*)

Biomarker	Rationale	Comments	Limitations
Fucosylated plasma glycans (D-glycan, GP30, or DG-9 index)[10,45]	Oligosaccharide chains (e.g., glycans) strongly influence protein−protein interactions and are involved in protein folding, sub-cellular targeting, and trafficking	Mutations in *HNF1A* result in marked alterations of plasma glycan profile	The performance of antennary fucosylation as a biomarker for *HNF1A*-MODY could be influenced by inflammatory events
	Glycans have been used as biomarkers to screen for certain pathological conditions, monitor patients, or predict the occurrence of certain diseases	*HNF1A* gene, encoding for a transcription factor *HNF1α*, which is a master regulator of plasma protein fucosylation	Reproducibility of glycan assay is poor
		In patients carrying a damaging mutation type in the *HNF1A* gene, fucosylated protein (DG-9 index and GP30) levels significantly decreased compared to the nonpathogenic and no mutation groups	
Low HDL-C levels[10]	Low HDL-C occur in patients with type 2 diabetes when compared with those with MODY	HDL-C levels can help to differentiate HNF1α-MODY, GCK-MODY, and type 1 diabetes from type 2 diabetes	Low serum levels of HDL-C may be detected in patients with *HNF4A*-MODY
Islet autoantibodies (GADA, IA2-A, IAA, and ZnT8A)[4,6,10,42]	Islet autoantigens (GAD65, IA-2A insulin, and ZnT8) along with genetic and environmental factors are implicated with the development of type 1 diabetes	Autoantibodies to islet autoantigens (GAD65, IA-2A, insulin, and ZnT8) are important biomarkers of type 1 diabetes and to distinguish type 1 diabetes from MODY and other diabetes forms	Except for GADA, islet autoantibodies are detected in the first few months from disease onset in pediatric type 1 diabetes patients rather than adults
			GADA is mostly detected in adult-onset type 1 diabetes and LADA cases and usually remains in circulation for several years from disease onset
			A low titer of positive IA2-A has been reported in rare cases of MODY
Sensitivity to sulfonylureas[10,42]	Sulfonylureas are potent antihyperglycemic drugs used in patients with type 2 diabetes	Patients with *HNF1A*-MODY and *HNF4A*-MODY are extremely sensitive to sulfonylureas, and both respond well to low-dose sulfonylureas	Sensitivity to sulfonylureas may be varied individually
			Cases with *ABCC8*-MODY and *KCNJ11*-MODY require high-dose sulfonylureas

1,5-AG, 1,5-anhydroglucitol; ApoM, apolipoprotein M; C5, complement factor 5; C8, complement factor 8; ESKD, end-stage renal disease; GADA65, glutamic acid decarboxylase-65; GCK, glucokinase; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin A1c; DG-9, Glycan groups GP30, GP36, and GP38; DG-9 index, desialylated glycan 9 index; HDL-C, high-density lipoprotein cholesterol; *HNF4A*, hepatocyte nuclear factor-4 alpha; *HNF1B*, hepatocyte nuclear factor-1 beta; hs-CRP, high-sensitivity C-reactive protein; IA2-A, islet antigen 2; IAA, insulin antibody; LADA, latent autoimmune diabetes in adults; MODY, maturity-onset diabetes of the young; SGLT2, sodium-glucose linked co-transporter 2; TTR, transthyretin; UCPCR, urinary C peptide to creatinine ratio; ZnT8, zinc transporter 8.

birth weight will be normal; (3) if the mother is normoglycemic but the father carries a pathogenic *GCK* variant and this variant has been transmitted to the fetus, as the mother's blood glucose levels will be insufficient to stimulate fetal insulin secretion and maintain optimal growth, the baby will be at increased risk of low birth weight; and (4) finally, if the mother is normoglycemic and the father carries a pathogenic *GCK* variant that is not transmitted to the fetus, then fetal insulin secretion and normal birth weight are expected.[5,20] Thus, insulin therapy should be considered in a pregnant woman with GCK-MODY only when marked maternal hyperglycemia occurs or accelerated fetal growth is observed on ultrasonography.[42] It is estimated that approximately 5% of women with gestational diabetes may carry a pathogenic mutation that causes MODY; therefore, genetic testing is recommended to all women with gestational diabetes.

Although diabetes in patients with *HNF4A*- or *HNF1A*-MODY is initially managed with lifestyle modification alone, patients may be exposed to postprandial hyperglycemia when they consumed foods rich in carbohydrates.[4] But over time, beta cells progressively deteriorate, and most patients may require treatment. Generally, patients tend to respond well to a low-dose sulfonylurea or a glinide.[5,8] Alternatively, a GLP-1 receptor analog (GLP-1RA) may be used. A randomized controlled trial comparing GLP-1RA and glimepiride in *HNF1A*-MODY patients demonstrated that both drugs were comparable in lowering blood glucose levels (although the potence of glimepiride was slightly higher and the risk of hypoglycemia was greater).[5]

Patients with *HNF1B*-MODY generally do not respond well to sulfonylureas due to accompanying pancreatic hypoplasia or hepatic

Box 2. Main Components of the MODY Probability Calculator	
1. Age at diagnosis	—— years
2. Sex	○ Male ○ Female
3. Currently treated with insulin and/or OADs?	○ Yes ○ No
4. Time to insulin treatment (if currently treated with insulin)	○ Not currently treated with insulin ○ Within 6 months of diagnosis ○ Over 6 months after diagnosis
5. BMI	——.—— kg/m^2
6. HbA1c	——.—— % (——.—— mmol/mol)
7. Current age	—— years
8. Parent(s) affected with diabetes?	○ Yes ○ No
9. Ethnicity	○ White ○ Non-white
10. Other	○ Renal cysts ○ Deafness ○ Partial lipodystrophy ○ Severe insulin resistance in absence of obesity ○ Severe obesity with other syndromic features

Available at https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator. Accessed on March 17, 2023. BMI, body mass index; HbA1c, glycated hemoglobin A1c; maturity-onset diabetes of the young; OAD, oral antidiabetic drug.

insulin resistance.[5,24,37] Therefore, patients often need insulin to control hyperglycemia. Patients may develop end-stage kidney disease (ESKD) independent of nephropathy as the mutated gene affects the kidneys during organogenesis.[37] Monitoring of renal function is recommended since most patients will develop kidney failure by the age of 45.[24]

The treatment of rarer MODY subtypes, particularly *IPF1/PDX1-*, *CEL-*, *INS-*, and *APPL1*-MODY, relies solely on insulin, whereas, *ABCC8*-MODY patients tend to respond to high-dose sulfonylureas. Newer drugs have been also tried in a limited number of cases. A case with *ABCC8*-MODY has been treated with dapagliflozin, a sodium-glucose linked co-transporter 2 inhibitor in combination with a sulfonylurea; another case with *IPF1/PDX1*-MODY was treated with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor. Moreover, rosiglitazone, a thiazolidinedione combined with sitagliptin has been used in patients with *HNF1A*-MODY.[25]

In general, guidelines for other MODY subtypes are not available due to the small number of cases. Metformin and insulin are the main medications approved for use in young people. In some countries, sulfonylureas are also approved for use in adolescent population. Apart from these, no drug in the OAD category has been in use by MODY cases younger than 18 years.

Characteristic Peculiarities of Maturity-Onset Diabetes of the Young Subtypes

Table 2 shows the nomenclature used for MODY subtypes, defective genes, gene functions, tissue expressions, clinical features, mode of inheritance, precision treatment, complications, and monitoring details.

HNF4A-MODY (Formerly MODY1)

HNF4A-MODY is thought to be less commonly encountered than *HNF1A*-MODY or GCK-MODY. *HNF1A* and *HNF4A* genes are responsible for regulating the expression of several genes encoding serum proteins including Apos and clotting factors.[5,44] If the patient has

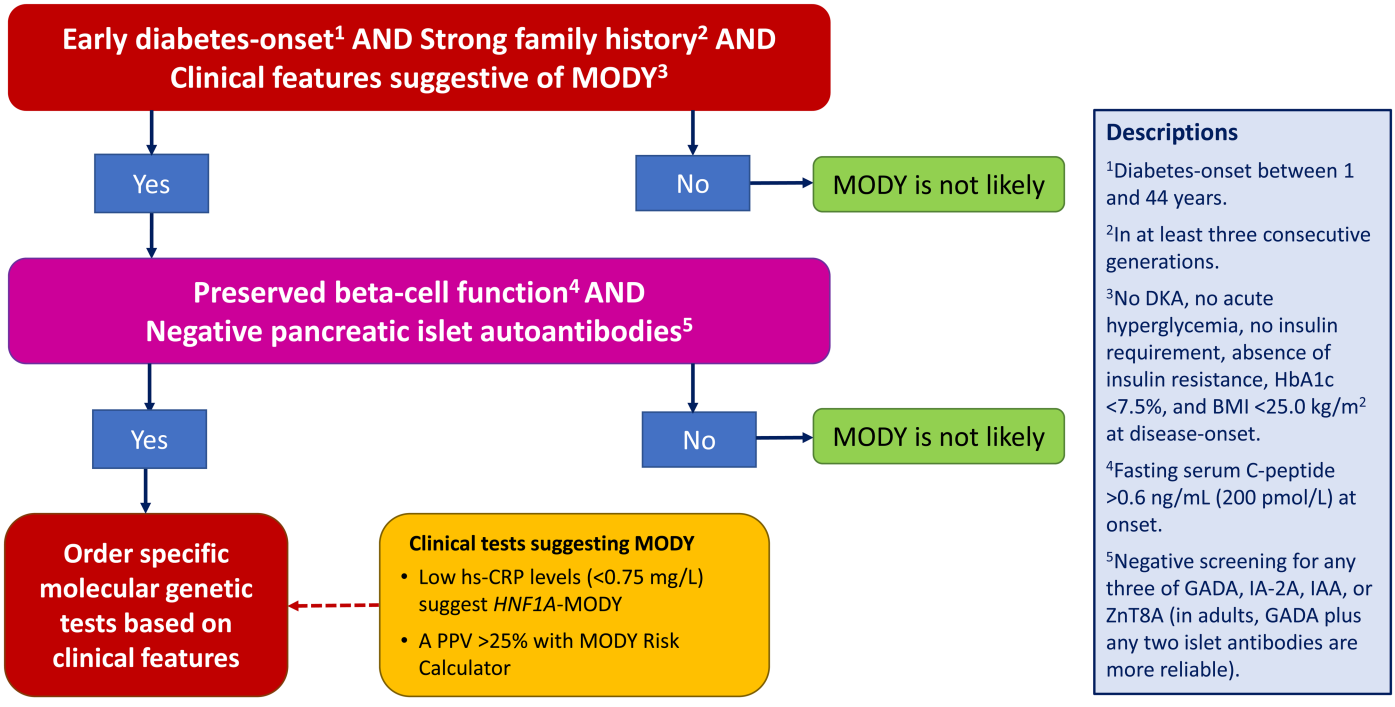

Figure 1. Diagnostic algorithm in patients suspected for MODY.[4,5,7,8,47,48] BMI, body mass index; DKA, diabetic ketoacidosis; GADA, IA2-A, IAA, and ZnT8A, autoantibodies to glutamic acid decarboxylase-65, islet antigen-2, insulin, and zinc transporter 8; hs-CRP, high-sensitivity C-reactive protein; MODY, maturity-onset diabetes of the young; PPV, positive predictive value.

features compatible to *HNF1A*-MODY but the genetic test is found negative, then one should screen for *HNF4A*-MODY. In addition, since *HNF4A* is expressed in the liver, patients may have dyslipidemia with low HDL-C and high triglyceride levels and develop metabolic syndrome;[24] thus, they are similar to type 2 diabetes. Furthermore, women with *HNF4A*-MODY may have a high incidence of macrosomia and transient neonatal hypoglycemia. These patients are very sensitive to sulfonylureas.[5,24]

GCK-MODY (Formerly MODY2)

Glucokinase is an enzyme that enables beta cells and hepatocytes to sense glucose. As the glucose threshold to induce insulin secretion is reset in GCK-MODY, fasting glucose levels are mildly elevated. Oral glucose tolerance test exhibits a mild increase in glucose concentration. Patients with *GCK* mutation are typically asymptomatic and reveal mild but nonprogressive hyperglycemia. Average HbA1c is generally less than 7.5% (59 mmol/mol), with a low risk of micro- and macrovascular complications.[5,24,47]

HNF1A-MODY (Formerly MODY3)

Mutations in the *HNF1A* gene inhibit mitochondrial metabolism, glucose transport, and beta-cell metabolism. *HNF1A* is expressed in hepatic, renal, intestinal, and pancreatic cells. In addition, the threshold for glycosuria is reduced. Cases of *HNF1A*-MODY are usually diagnosed between the ages of 20 and 25 years. Penetration of the mutated gene is high. About 96% of carriers develop diabetes by the age of 45 years.[24] Beta cells do not respond adequately to hyperglycemia, and beta-cell dysfunction is progressive. However, these patients are highly sensitive to sulfonylureas or glinides.[5] Similar to type 1 and type 2 diabetes, patients have an increased risk of microvascular and macrovascular complications.[24] Despite that, HDL-C is typically elevated, and they are particularly predisposed to CVD. Therefore, initiation of statin therapy before the age of 40 is mandatory. In addition, hs-CRP is classically lower in *HNF1A*-MODY than other forms of diabetes, making it a reliable potential biomarker. Some cases may reveal pancreatic exocrine dysfunction.[7,43]

PDX1/IPF1-MODY (Formerly MODY4)

Mutations in the *IPF1/PDX1* gene lead to a rare MODY subtype. The *PDX1* gene encodes a homeobox-containing transcription factor necessary in regulating pancreas development and function.[25] It is also involved in insulin (*INS*) gene expression. *IPF1/PDX1*-MODY has been reported in a few families from Türkiye, Brazil, Trinidad-Tobago, Italy, Sweden, India, and China.[20,25] The onset of diabetes ranges between 2 and 35 years without sex difference. Diabetes is usually mild.[4,25] Obesity and hypertension have been reported rarely.[20] Coexistence of PDX1/IPF1-MODY and *HNF1A*-MODY in some families suggests that *HNF1A* is a modifying gene. Compared to neonatal diabetes due to *IPF1/PDX1* mutation, pancreatic agenesis is relatively rare in this form of MODY[9]; exocrine pancreatic insufficiency is marked by decreased fecal elastase.[24] A large number of patients are treated with insulin. *IPF1/PDX1* mutation may disrupt the incretin pathway, and DPP-4 inhibitors (sitagliptin) may be useful.[25] Complications (mild non-proliferative retinopathy) are rare in PDX1/IPF1-MODY patients.[25]

HNF1B-MODY (Formerly MODY5)

HNF1B-MODY is responsible for 5%-10% of all MODY cases and may represent a wide range of clinical pictures.[24,37] Almost half of the cases are characterized with early-onset diabetes. Mutation in *HNF1B* disturbs gene regulation in renal, pancreatic, hepatic, intestinal, ovary, and lung cells. Pancreatic dysplasia or atrophy, elevated liver enzyme levels, and kidney cysts, hypoplastic glomerulocystic kidneys, and urinary tract malformations are commonly seen.[8,20,37,47] When accompanied with renal cysts, it is called renal cysts and diabetes syndrome. There is a progressive loss of renal function independent of diabetic nephropathy.[20] Hypomagnesemia, hyperuricemic nephropathy, gout, and primary hyperparathyroidism may accompany this syndrome.[24,37] Mutation in *HNF1B* has also been implicated with genital anomalies such as bicornate uterus, Rokitansky syndrome, vas deferens agenesis, and hypospadias.[24] Patients may develop neuropsychiatric problems, including intellectual disability and autism. Babies born with *HNF1B* mutations may have low birth weight due to decreased intrauterine insulin secretion. Rarely, signs of insulin resistance may be seen. Patients generally do not respond to OADS, and insulin therapy is required in most cases.[5] Microvascular complications are relatively common.[37]

NEUROD1-MODY (Formerly MODY6)

It is a basic–loop–helix transcription factor required for insulin synthesis and secretion. *NEUROD1* also acts on pancreatic and neuronal development.[24,25] *NEUROD1*-MODY has been reported from Japan, China, Thailand, India, Iceland, Czech Republic, and Poland.[9,20,24,32,40] The age at onset ranges between 10 and 33 years, more common among women than men.[9,20,25] There are some cases with maternal transmission, and carrier mothers may have gestational diabetes.[25,32] These cases may have recurrent episodes of DKA, which is rarely present among other MODY subtypes. Hearing loss, learning disabilities, convulsions, mental retardation, and hippocampal hypoplasia are rarely reported.[10,24,25] Few cases may present with obesity.[32] Treatment of diabetes requires insulin in most of the cases. Few patients can be treated with OADs alone. Alpha glucosidase inhibitors and DPP-4 inhibitors may be beneficial when added to insulin in some cases.[25,40] Microvascular complications (retinopathy, nephropathy, and neuropathy) are frequently reported, and few patients died of chronic renal failure.[25]

KLF11-MODY (Formerly MODY7)

KLF11 controls *PDX1* transcription in pancreatic beta cells. It was first reported in several families with early-onset type 2 diabetes.[9,20,25,31] Some patients with this mutation may be overweight or obese,[36] with high low-density lipoprotein cholesterol and triglyceride levels. Some patients were treated with metformin and rosiglitazone (a thiazolidinedione), and no complications were reported.[25]

CEL-MODY (Formerly MODY8)

The CEL-MODY has been reported in few families from Norway, Denmark, Siberia, China, and Türkiye.[9,20,25] Besides diabetes, patients may have clinical manifestations of exocrine pancreas involvement.[25] Insulin is the treatment of choice.[10,20,25] Microvascular complications, mainly non-proliferative diabetic retinopathy, peripheral neuropathy, and a biopsy-proven diabetic kidney disease with high albumin-to-creatinine ratio, have been reported.[25]

PAX4-MODY (Formerly MODY9)

PAX4-MODY has been described in several families from Japan, Singapore, China, India, Thailand, and Siberia.[25,31] The age of onset varied from 6 to 44 years, and it is more common in men than women. Insulin is the only treatment in most of the patients.[20,25] Diabetes may be severe and presented with DKA. Diabetic retinopathy and nephropathy have been reported. The early-onset renal complication may lead to ESKD and death.[25,10]

Table 2. MODY Subtypes, Gene Function, Tissue Expression, Clinical Phenotypes, Inheritance, Precision Treatment, Complications, and Monitoring

MODY Subtype (Former Nomenclature)	Affected Gene	Gene Function and Tissue Expression	Pathophysiology	Clinical Features	Mode of Inheritance	Precision Treatment	Diabetes Complications and Monitoring
HNF4A-MODY (MODY1)[5,10,24,25,47]	Hepatocyte nuclear factor-4 alpha	Transcription factor (nuclear factor) Expressed in pancreatic beta, kidney, liver, and intestinal cells as well as insulinoma cell lines	Pancreatic beta-cell dysfunction Neonatal hyperinsulinemia Progressive insulin secretion defect	Neonatal diabetes Macrosomia Hyperinsulinemic hypoglycemia MODY Low serum levels of HDL-C, triglycerides, Apo-A1, and Apo-A2 Impaired glucagon secretion Fanconi syndrome Nephrocalcinosis, hypercalciuria	Autosomal dominant	Diet and low-dose sulfonylureas (very sensitive to sulfonylureas) Some patients may require insulin later	Microvascular complications are less common. Monitoring for complications in kidneys and retina
GCK-MODY (MODY2)[5,10,24,25]	Glucokinase (hexokinase 4)	First step enzyme catalyzing the glycolytic pathway Expressed in pancreatic beta and liver cells	Glucose sensing defect Fasting hyperglycemia from newborn	Stable, mild fasting hyperglycemia Small incremental increase between fasting and 2-hPG on OGTT (usually <63 mg/dL (3.5 mmol/L) HbA1c >7.5% (59 mmol/mol) No additional pancreatic anomalies Rarely obesity	Autosomal dominant Rarely autosomal recessive	Diet No pharmacologic treatment is needed except during pregnancy (depending on the fetal inheritance may require insulin) Permanent neonatal hypoglycemia	Complications are rare
HNF1A-MODY (MODY3) [5,10,24,25]	Hepatocyte nuclear factor-1 homeobox alpha	Transcription factor Expressed in liver, pancreatic islet, and kidney cells	Pancreatic beta-cell dysfunction Progressive insulin secretion defect Impaired renal glucose transport	Large incremental increase between fasting and 2-hPG on OGTT DKA Lower renal glucose absorption threshold (glycosuria) Low hs-CRP Increased HDL-C levels	Autosomal dominant	Diet and low-dose sulfonylureas or glinides (very sensitive to sulfonylureas) Some patients may require insulin later GLP-1RAs and SGLT2 inhibitors may be effective	Common (renal and retinal) microvascular complications Increased risk of macrovascular complications Monitoring for CVD risk factors and liver enzymes
PDX1/IPF1-MODY (MODY4)[4,21,24,25]	Pancreatic and duodenal homeobox 1/ insulin promoter factor 1	Transcription factor (homeodomain) Expressed in pancreatic beta cells	Pancreatic beta-cell dysfunction Pancreatic agenesis	Rare Permanent or transient neonatal diabetes MODY with mild diabetes DKA Azoospermia Renal cysts Uterine anomalies Other genitourinary malformations Some patients may be overweight or obese	Autosomal recessive Rarely autosomal dominant	Diet, OADs (sulfonylureas, metformin, or DPP-4 inhibitors) Cases with autosomal-dominant inheritance may require insulin treatment	Unknown

(*Continued*)

Table 2. MODY Subtypes, Gene Function, Tissue Expression, Clinical Phenotypes, Inheritance, Precision Treatment, Complications, and Monitoring (*Continued*)

MODY Subtype (Former Nomenclature)	Affected Gene	Gene Function and Tissue Expression	Pathophysiology	Clinical Features	Mode of Inheritance	Precision Treatment	Diabetes Complications and Monitoring
HNF1B-MODY (MODY5) [5,8,20,21,24,37,47]	Hepatocyte nuclear factor-1 homeobox beta	Transcription factor (homeodomain)-regulating insulin gene Expressed in the gut, thymus, liver, lung, kidney, and bile duct cells	Pancreatic beta-cell dysfunction Exocrine pancreas dysfunction Renal and genital anomalies	Pancreatic hypoplasia or atrophy Renal deformities (horseshoe kidney and RCAD syndrome), early (<45 years of age) renal failure, hyperuricemia, gout Increased liver enzymes Anomalies of the female genitalia Azoospermia Reduced birth weight Transient neonatal hypoglycemia	Autosomal dominant Rarely spontaneous	Insulin Some cases may respond to sulfonylureas or glinides GLP-1RAs may be effective Magnesium supplements	Complications are common (early ESKD independent of diabetic nephropathy) Monitoring renal, urinary, genital, gonadal, and exocrine pancreatic functions by a multidisciplinary team
NEUROD1-MODY (MODY6) +	Neurogenic differentiation 1	Transcription factor (BHLH) Expressed in intestinal, CNS, neuronal, and pancreatic endocrine cells	Pancreas abnormalities Neurologic impairments	Rare Permanent neonatal diabetes Adult- or childhood-onset diabetes DKA Rare cases with obesity	Autosomal recessive Rarely autosomal dominant	Diet and OADs Some patients may require insulin	Mild-to-severe microvascular complications (proliferative retinopathy and kidney failure) in adults, neonates, and children Neurologic abnormalities
KLF11-MODY (MODY7) [9,21,25]	Kruppel-like factor 11 (*TGF-β*)	Transcription factor Ubiquitously expressed	Decreased insulin sensitivity	Pancreatic malignancy, pancreatic atrophy, and exocrine dysfunction Mild hyperglycemia similar to type 2 diabetes Some cases with overweight or obesity	Autosomal dominant	OADs Some patients may require insulin	Unknown
CEL-MODY (MODY8) [9,10,21,25]	Carboxyl ester lipase	Enzyme controlling pancreatic exocrine and endocrine functions Responsible for misfolding proteins Expressed in lactating mammary gland and pancreatic cells	Exocrine pancreas dysfunction and malabsorption	Exocrine and endocrine pancreatic dysfunction Pancreatic atrophy Lipomatosis and fibrosis Diabetes with moderate-to-severe hyperglycemia	Autosomal dominant VNTR deletion	Diet and OADs Frequently requires insulin	Unknown Monitoring exocrine pancreatic functions

(*Continued*)

Table 2. MODY Subtypes, Gene Function, Tissue Expression, Clinical Phenotypes, Inheritance, Precision Treatment, Complications, and Monitoring (*Continued*)

MODY Subtype (Former Nomenclature)	Affected Gene	Gene Function and Tissue Expression	Pathophysiology	Clinical Features	Mode of Inheritance	Precision Treatment	Diabetes Complications and Monitoring
PAX4-MODY (MODY9) [10,25,31]	Paired box 4	Transcription factor Expressed in embryonic germ cells in mammals	Cancer growth Fetal development Pancreatic beta-cell dysfunction	Extremely uncommon Progressive hyperglycemia (adult-onset diabetes) DKA likely Some cases with overweight or obesity Aniridia	Autosomal dominant	Diet and OADs Some patients may require insulin	Unknown
INS-MODY (MODY10) [10,23,25,30,36,41]	Insulin	Encodes insulin precursors Insulin gene mutations Responsible for misfolding proteins Expressed in pancreatic, limb, and eye cells	Defective insulin biosynthesis Regulates beta-cell activity ER stress	Extremely uncommon Permanent neonatal diabetes Adult-onset diabetes (>20 years of age) Mild DKA PCOS Cataract Bipolar disorder	Autosomal dominant	Diet and early intensive insulin treatment Some cases may respond to OADs (sulfonylureas)	Retinopathy, neuropathy
BLK-MODY (MODY11) [9,10,21,25]	B-lymphoid tyrosine kinase	Tyrosine kinase functions in signal transduction (B-cell specific) Expressed in muscle, ovary, pancreatic islets, testis, and spleen cells as well as lymphoblastoid cell lines	Defective insulin secretion	Extremely uncommon Increased penetrance with higher BMI (some patients may be overweight or obese)	Autosomal dominant	Diet and OADs Some patients may require insulin	Unknown
ABCC8-MODY (MODY12) [9,10,21,24,25,33,50]	ATP-binding cassette subfamily C (CFTR/MRP), member 8	Regulates insulin release by linking cellular metabolism to electrical activity of plasma membrane Expressed in pancreatic beta cells	Defective insulin secretion due to K-ATP channel dysfunction	Permanent or transient diabetes Rare MODY cases Clinical phenotype similar to *HNF1A/HNF4A* Hyperinsulinemic hypoglycemia Developmental delay Epilepsy	Autosomal dominant	Diet and high-dose sulfonylureas Frequently requires insulin	Unknown Monitoring neurodevelopment
KCNJ11-MODY (MODY13) [9,21,25]	Potassium channel, inwardly rectifying subfamily J, member 11	Regulates glucose-induced insulin secretion in pancreatic beta cells Expressed in muscle, pancreatic beta, and neuronal cells	Defective insulin secretion	Uncommon Clinical phenotype heterogeneous Homozygous permanent or transient neonatal diabetes Neonatal hyperinsulinemic hypoglycemia Developmental delay Epilepsy	Autosomal dominant	Diet and high-dose sulfonylureas Frequently requires insulin	Unknown Monitoring the neurodevelopment

(*Continued*)

Table 2. MODY Subtypes, Gene Function, Tissue Expression, Clinical Phenotypes, Inheritance, Precision Treatment, Complications, and Monitoring (*Continued*)

MODY Subtype (Former Nomenclature)	Affected Gene	Gene Function and Tissue Expression	Pathophysiology	Clinical Features	Mode of Inheritance	Precision Treatment	Diabetes Complications and Monitoring
APPL1-MODY (MODY14) [25]	Adaptor protein, phosphotyrosine interaction, pH domain, and the leucine zipper 1	Insulin signal transduction Expressed in heart cells; elevated expression in skeletal muscles, pancreas, and ovary	Defective insulin secretion	Childhood or adult-onset diabetes Some patients may be overweight or obese Rarely manifest with DIDMOAD syndrome	Autosomal dominant	Diet and OADs Frequently requires insulin	Unknown
WFS1[25]	Wolframin	ER calcium channel	ER stress, beta-cell dysfunction	DIDMOAD syndrome Neurologic and neuropsychiatric manifestations	Autosomal-recessive	Diet and insulin	Neuropathy and eye complications independent of diabetic microvascular complications Monitoring by a multidisciplinary team
RFX6[23,25,49]	Regulator factor X6 (UK, Finland, Japan)	Beta-cell transcription factor Expressed almost exclusively in pancreatic islets, small intestine, and colon	Regulates the differentiation and function of insulin-producing beta cells Reduced GIP secretion	GIP deficiency Reduced penetrance of MODY Homozygous may cause neonatal diabetes	Autosomal-recessive Autosomal dominant (dominant protein truncating variant)	Diet and OADs (DPP-4 inhibitors) or GLP-1RAs Not sensitive to sulfonylureas Some cases may require insulin	Unknown
NKX6-1[25,50]	NK6 homeobox 1 (India)	Homeobox protein Expressed in gastric mucosa, pancreatic islet, exocrine pancreas, endometrium, thyroid, and CNS cells	Development of beta cells	Normal glycemia or mild diabetes	Autosomal recessive	Not reported	Unknown

2-hPG, 2-hour plasma glucose; Apo, apolipoprotein; ATP, adenosine triphosphate; BHLH, basic helix–loop–helix; BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CVD, cardiovascular disease; CNS, central nervous system; DIDMOAD, diabetes insipidus, diabetes mellitus, optical atrophy, and deafness; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl-peptidase 4; ER, endoplasmic reticulum; ESKD, end-stage renal disease; GCK, glucokinase; GIP, glucose-independent insulinotropic peptide (formerly gastric inhibitory polypeptide); GLP-1RAs, glucagon-like peptide 1 receptor analogs; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; *HNF1A*, hepatocyte nuclear factor 1 alpha; hs-CRP, high-sensitivity C-reactive protein; IPF1, insulin promoter factor 1; K-ATP, adenosine triphosphate-sensitive potassium; MODY, maturity-onset diabetes of the young; MRP, multidrug resistance; OAD, oral antidiabetic drug; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PDX1, pancreatic duodenal homeobox 1; RCAD, renal cyst and diabetes; SGLT2, sodium-glucose linked co-transporter 2; TGF-β, transforming growth factor beta; VNTR, variable number tandem repeat.

INS-MODY (Formerly MODY10)

INS-MODY has been reported in some families from Norway, Denmark, Czech Republic, France, Italy, USA, Japan, China, and Australia.[25,30,36,41] While the *INS* heterogeneous mutation is detected as the dominant MODY type in some populations, there are a few reported cases of INS-MODY in some populations (e.g., Türkiye).[9,20] The mean age in diabetes onset is 13.7 years. The misfolded protein results in endoplasmic reticulum stress and beta-cell destruction. The phenotype in dominant *INS* mutation generally resembles type 1 diabetes. However, clinical presentation of diabetes may vary from mild form to rare cases with gestational diabetes, early-onset diabetes, and DKA.[25] The treatment is changed. *INS*-MODY patients can be treated with OAD only, OADs plus insulin, or insulin alone according to the clinical presentation.[10,25] Complications include mild proliferative retinopathy, microalbuminuria, nephropathy, and peripheral neuropathy.[25] Polycystic ovary syndrome has been described rarely.[25]

BLK-MODY (Formerly MODY11)

BLK gene is necessary for insulin synthesis and secretion. Mutations identified in this gene are rarely reported in the literature.[9,20,25] Obesity may be present in some families with the BLK-MODY.[10] Most patients were treated with insulin. No complications have been reported in this MODY subtype.[25]

ABCC8-MODY (Formerly MODY12)

Heterozygous mutations in *ABCC8* are one of the causes of MODY.[10,25] *ABCC8*-MODY has been identified in families across the world.[9,20,25,33,50] The mean age at diabetes onset is 17.3 years with no gender difference. Obesity was reported in few cases.[20] Similar to *HNF1A*-MODY and *HNF4A*-MODY, these patients respond well to sulfonylureas.[25] A mild form of diabetes was reported in some families with *ABCC8*-MODY.[25] Mild developmental delay and mental retardation have been linked with rare variants. According to a report from South India, *ABCC8* is one of the most commonly mutated MODY gene from the region.[26,50] A large number of patients were treated with sulfonylureas and metformin. Few patients used dapagliflozin.[24,25] Microvascular (peripheral neuropathy, pre-proliferative retinopathy, and nephropathy) and macrovascular (atherosclerosis) complications, hypertension, dyslipidemia, and convulsive seizures have been reported.[25]

KCNJ11-MODY (Formerly MODY13)

KCNJ11 gene mutations have been associated with many diseases including permanent or transient neonatal diabetes; if transient, diabetes often recurs later in life. Some cases may be recognized for the first time with neonatal hypoglycemia. In this case, monitoring fetal growth and blood glucose levels in newborns is crucial. *KCNJ11*-MODY has been identified in a limited number of families from Denmark, Türkiye, and Singapore.[9,20,25] Patients generally well respond to sulfonylureas and insulin. Complications were not reported.

APPL1-MODY (Formerly MODY14)

APPL1 mutations were reported in families from Italy and the USA.[25] Diabetes is treated with insulin and/or OADs. Complications were not reported. Earlier reports linked *APLL1*-MODY with DIDMOAD syndrome.

Candidate Maturity-Onset Diabetes of the Young Genes

During the recent years, mutations in the *WFS1*,[25] *RFX6*,[49] and NKX6-1[50] genes with clinical features similar to MODY have been reported in a limited number of cases, allowing these genes to be included in MODY candidate genes.

Conclusion

In MODY, defective genes can affect insulin secretion through impaired insulin sensing and glucose metabolism or activation of K-ATP channels. The clinical picture in MODY cases is quite heterogeneous. The same mutations in a particular gene may present with different clinical manifestations in diverse populations and ethnic groups, or even within the same family.

Maturity-onset diabetes of the young patients should be followed by an interdisciplinary team consisting of an endocrinologist or internist, a diabetes nurse, a dietitian, and a medical geneticist. In specific situations, contributions of other experts (i.e., in *HNF1B*-MODY cases ophthalmologist, nephrologist, gynecologist, and cardiologist) may be required. Except for patients with *GCK* mutations and some rare newer MODY subtypes, these patients are prone to chronic complications similar to other diabetes patients. Therefore, routine screening for complications should not be neglected.

As a result, our current knowledge is not yet sufficient for most newly identified MODY subtypes. Large and multi-ethnic longitudinal studies are needed to distinguish MODY subtypes from other forms of diabetes, to develop mutation-specific clinical biomarkers, and to offer precision treatment. Increasing the awareness of healthcare professionals about MODY will be beneficial especially for referral to expert centers and timely diagnosis.

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