Review article

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Maturity-onset diabetes of the young (MODY): an update

Abstract: Maturity-onset diabetes of the young (MODY) is a group of monogenic disorders characterized by autosomal dominantly inherited non-insulin dependent form of diabetes classically presenting in adolescence or young adults before the age of 25 years. MODY is a rare cause of diabetes (1% of all cases) and is frequently misdiagnosed as Type 1 diabetes (T1DM) or Type 2 diabetes (T2DM). A precise molecular diagnosis is essential because it leads to optimal treatment of the patients and allows early diagnosis for their asymptomatic family members. Mutations in the glucokinase (*GCK)* (MODY 2) and hepatocyte nuclear factor (*HNF)1A/4A* (MODY 3 and MODY 1) genes are the most common causes of MODY. *GCK* mutations cause a mild, asymptomatic, and stable fasting hyperglycemia usually requiring no specific treatment. However, mutations in the *HNF1A* and *HNF4A* cause a progressive pancreatic β-cell dysfunction and hyperglycemia that can result in microvascular complications. Sulfonylureas are effective in these patients by acting on adenosine triphosphate (ATP)-sensitive potassium channels, although insulin therapy may be required later in life. Mutations in the *HNF1B* (MODY 5) is associated with pancreatic agenesis, renal abnormalities, genital tract malformations, and liver dysfunction. Compared to MODY 1, 2, 3, and 5, the remaining subtypes of MODY have a much lower prevalence. In this review, we summarize the main clinical and laboratory characteristics of the common and rarer causes of MODY.

Keywords: children; hyperglycemia; maturity-onset diabetes of the young; pancreatic β-cell.

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Introduction

Maturity-onset diabetes of the young (MODY) is an autosomal dominantly inherited type of diabetes that results from heterozygous mutations in various transcription factors acting in the development and maturation of pancreatic β-cells (1). In addition, mutations in enzymes involved in glucose sensing of the β-cell have also been shown to result in early-onset diabetes (2). Characteristic features of MODY are autosomal inheritance, early onset of diabetes (with diagnosis generally before the age of 25 years), no signs related to the autoimmune process or insulin resistance, and preservation of endogenous insulin secretion (3, 4).

History and prevalence

In 1974, Tattersall et al. (5) reported on a family with dominantly inherited, mild diabetes mellitus. The group defined the molecular and clinical characteristics of the disease, using the name of "maturity-onset–type diabetes of young people (MODY)" for the first time (6). The molecular genetics of this disease were first defined in the 1990s, with mutations in the genes encoding glucokinase (GCK) (1992), hepatocyte nuclear factor (HNF) 4α and HNF1α (1996), insulin promoter factor (1997), and HNF1β (1997) shown, for the first time, to cause MODY (1). With the more recent identification of novel genes, more than 10 genes are currently known to cause MODY (7).

MODY is reported to be the most common form of monogenic diabetes and affects 1–2% of all diabetic patients in Europe (8). Recent studies have reported a MODY prevalence of 21–45/1,000,000 children and 100/1,000,000 adults (9–11). It has been determined that 5% of individuals diagnosed with diabetes before the age of 45 years have MODY, with 80% of individuals misdiagnosed as having type 1 (T1DM) or type 2 diabetes mellitus (T2DM) (12). In addition, a childhood study reported that 36% and 51% of individuals misdiagnosed with T1DM and T2DM, respectively, actually had MODY (11).

Genetics

Mutations in many genes with a role in pancreatic β-cell development or insulin secretion can cause MODY. Genes that are known to cause MODY are those encoding (13–18):

- *HNF4A* (MODY 1)
- glucokinase [*GCK* (MODY 2)]
- HNF1α [*HNF1A* (MODY 3)]
- pancreatic and duodenal homeobox 1 [*PDX1/IPF* (MODY 4)]
- HNF1β [*HNF1B* (MODY 5)]
- neurogenic differentiation 1 [*NEUROD1* (MODY 6)]
- Krüppel-like factor 11 [*KLF11* (MODY 7)]
- carboxyl ester lipase [*CEL* (MODY 8)]
- paired box gene 4 [*PAX4* (MODY 9)]
- insulin [*INS* (MODY 10)]
- B-lymphocyte kinase [*BLK* (MODY 11)]
- ATP -binding cassette, subfamily C, member 8 [*ABCC8* (MODY 12)]
- potassium channel, inwardly rectifying, subfamily J, member 11 [*KCNJ11* (MODY 13)].

Novel MODY-causing genes are still being defined, and their roles in the pathogenesis of diabetes are being investigated (19). It is believed that many MODY-related genes have not yet been identified (20).

Mutations in the *GCK*, *HNF1A*, *HNF4A*, and *HNF1B* genes are the most common causes of MODY in the UK, and they represent 32%, 52%, 10%, and 6% of MODY cases, respectively (13). However, the causes of MODY can differ between countries, with these differences potentially related to the use of screening programs, which also detect asymptomatic individuals. *GCK* mutations have been reported to be the most common cause of MODY in Spain, France, and Italy, where routine blood glucose screening is performed, whereas in countries where routine blood glucose tests are seldom done, *HNF1A*-MODY is more commonly diagnosed (7). In addition, the age of the enrolled individuals might affect the mutation distribution. While *GCK* mutations were rare (12%) in a Norwegian cohort, which included adults, they were more common (41–63%) in two large studies conducted with children in Italy (2).

Genes causing MODY and their clinical characteristics are summarized in Table 1.

Specific subtypes and their properties

GCK-MODY (MODY 2)

Glucokinase, which serves as a key regulating enzyme in insulin secretion stimulated by glucose, acts as the

Table 1 MODY subtypes: gene mutations, pathophysiology, and clinical characteristics.

MODY	Gene	Pathophysiology	Clinical characteristics
1	*HNF4A*	Transcription factor; decreased insulin secretion	Rare (5%); neonatal hyperinsulinemia, low triglycerides, tendency for microvascular complications, sensitivity to sulfonylureas
2	*GCK*	Decreased glucose sensitivity due to phosphorylation defect; decreased glycogen storage	Common (30–50%); increased fasting glucose, increased likelihood of glucose <55 mg/dL on oral glucose tolerance test; mild diabetes that generally does not require anti-diabetes medication
3	*HNF1A*	Transcription factor; decreased insulin secretion, progressive β-cell damage	Common (30–50%), high penetrance; glycosuria, microvascular complications, sensitivity to sulfonylurea
4	*PDX1/IPF1*	Impaired pancreas development; homozygotes experience pancreas agenesis	Rare (1%); mean age at diagnosis 35 years, requires oral anti-diabetes treatment (and insulin)
5	*HNF1B*	Transcription factor; decreased insulin secretion	Rare (5%); extra pancreatic signs (renal cysts or dysplasia, genital abnormalities in females, azoospermia in males) with diabetes; variable phenotype; requires insulin treatment
6	*NEUROD1*	Abnormal development of β-cell functions	Very rare (<1%); adult-onset diabetes
7	*KLF11*	Tumor-suppressor gene; decreased glucose sensitivity of β-cells	Very rare (<1%); phenotype resembling type 2 diabetes
8	*CEL*	Decreased endocrine and exocrine pancreas functions (pathophysiology?)	Very rare (<1%); typically autosomal dominant diabetes
9	*PAX4*	Transcription factor affecting apoptosis and proliferation of β-cells	Very rare (<1%); possible ketoacidosis
10	*INS*	Heterozygous mutation of the insulin gene	Very rare (<1%); diabetes onset before 20 years of age; sulfonylurea or insulin treatment is generally required
11	*BLK*	Heterozygous mutation affecting insulin secretion	Very rare (<1%); increased penetrance with higher body mass indexes
12	*ABCC8*	ATP-sensitive potassium channels dysfunction	Very rare (<1%); clinical phenotype is similar to *HNF1A/4A*-MODY
13	*KCNJ11*	ATP-sensitive potassium channels dysfunction	Very rare (<1%); clinical phenotype is heterogenous

glucose sensor of pancreatic β-cells (2). To date, 620 mutations (missense, nonsense, frameshift, splice site, and promoter mutations and deletions) in 1441 families have been reported in the *GCK* gene, causing hypoglycemia and hyperglycemia (2).

Heterozygote-inactivating mutations of the *GCK* gene cause mild, subclinical hyperglycemia, which is generally present at birth and does not progress (2). The decrease in *GCK* activity in pancreatic β-cells caused by *GCK* mutations lead to decreased glucose phosphorylation and glucose sensitivity in β-cells, and a shift in the dose-response relationship between plasma glucose concentrations and insulin secretion to the right (21). A mild increase in fasting blood glucose is observed because of decreased hepatic glycogen synthesis and increased hepatic glucose production as a result of *GCK* mutations expressed in the liver (22). Although various mutations are observed in individuals with *GCK*-MODY, their phenotypic characteristics can show many similarities as unaffected alleles compensate for the mutations (2). As the result of an upward change in the required glucose concentration threshold to stimulate insulin secretion, fasting glucose levels show a mild increase (96–140 mg/dL) from birth (2).

Individuals with *GCK*-MODY are generally asymptomatic, so many are first diagnosed when their blood glucose levels are measured. It has been reported that 40–50% of children with asymptomatic or coincidental hyperglycemia have *GCK*-MODY (23, 24). These children are generally diagnosed during routine investigations or from blood glucose measurements performed to investigate another complaint (7). Children with *GCK*-MODY generally have a family history of T2DM or gestational diabetes history in their parents or grandparents. Because the mild hyperglycemia causes no symptoms, the parents of these children might not be known to have diabetes and, if mutation carriers, may be similarly diagnosed with mild fasting hyperglycemia and *GCK*-MODY (22, 25). Another laboratory characteristic that helps to differentiate *GCK*-MODY from other MODY subtypes is small increased glucose levels on an oral glucose tolerance test (OGTT) at minute 120. Overall, 70% of individuals with *GCK*-MODY have glucose levels below 54 mg/dL at this point, while 95% have levels below 83 mg/dL (26). Although not very common, individuals with glucose levels above 100 mg/dL at minute 120 have also been reported (27). It has been suggested that differences in blood glucose values measured by OGTT at minute 120 might be related to variations in insulin sensitivity among individuals with *GCK*-MODY (28).

Microvascular complications are rare in individuals with *GCK*-MODY, because the hyperglycemia is mild, and there is no marked progression (29, 30). In a study performed in France, it was reported that proliferative retinopathy, proteinuria, and peripheral neuropathy developed in 4–6% of these individuals (29). Furthermore, treatment with insulin or oral hypoglycemic agents might not result in a decrease in glycated hemoglobin (HbA_{1c}) levels (30). As hyperglycemia is developed due to defects in the recognition of glucose, the exogenous administration of low-dose insulin in these individuals results in decreased endogenous insulin secretion in compensation, and blood glucose levels remain unchanged. Decreases in blood glucose levels have been observed only when supraphysiological doses of insulin are given (30). Therefore, molecular confirmation of the diagnosis in these individuals will prevent unnecessary pharmacological treatments. Although there are no long-term data regarding macrovascular complications, it is believed that cardiovascular risk is increased in individuals with *GCK*-MODY (31). It has also been reported that these individuals can develop insulin resistance in the long term, which might negatively affect metabolic control (32).

The birth weight of a baby with *GCK*-MODY is related to the *GCK*-MODY status of both the child and its parents (33). If both the baby and the mother carry *GCK* mutations, then the increase in maternal blood glucose will lead to normal insulin in the baby; thus, the baby's birth weight will be within the normal range. If there is no mutation in the baby, then maternal hyperglycemia will cause an increase in insulin secretion in the child, which will lead to an approximately 500 g increase in the birth weight. On the other hand, if the baby has a *GCK* mutation inherited from the father, and the mother does not have the mutation, then insulin synthesis in the baby will be decreased, resulting in an approximately 500 g decrease in birth weight (33).

HNF1A-MODY (MODY 3)

To date, a total of 414 different mutations have been defined in 1247 families carrying the *HNF1A* gene (34). Although mutations can be observed in all exons, they are most often detected in exons 2 and 4. The most commonly reported mutations are missense mutations (55%), followed by frameshift (22%), splice site (9%), and promoter-region mutations (2%) and deletions (1.2%) (34). *HNF1A* is expressed in pancreatic β-cells, the liver, and intestines, and *HNF1A* is a critical transcription factor for *INS* and *GLUT2* (encoding a glucose carrier) in mature β-cells

(35, 36). *Hnf1a*-knockout mice have been shown to develop diabetes as a result of decreased insulin secretion (37).

HNF1A mutations are the most common causes of MODY in Europe, North America, and Asia (38). A C-nucleotide insertion in exon 4 (Pro291fsinsC) is the most widespread of up to 200 reported mutations (34). Heterozygous *HNF1A* mutations can cause diabetes with early-adulthood onset, via progressive β-cell dysfunction (39). A recent study reported that β-cell apoptosis was increased in individuals with *HNF1A* mutations, which stimulated the expression of the pancreatic stone protein/regenerating gene (PSP/reg) in surviving neighbor cells, with PSP/reg1A protein subsequently secreted from these cells (40). The genetic penetrance of *HNF1A* mutations is high, and 63% of individuals up to 25 years of age and 96% of those up to 55 years develop diabetes (34, 41). A correlation between mutation region and clinical phenotype has been reported, with individuals with exon 4–6 mutations showing signs of diabetes 8 years earlier (mean age 17 years) than those with exon 7–10 mutations (41).

The mean age of *HNF1A*-MODY diagnosis in children is 14 years (range 4–18 years), and it is rarely identified in children younger than 10 years (42). Although blood glucose is normal in the period before the appearance of diabetes, β-cell dysfunction can be observed (43). It has been shown that the insulinogenic index of individuals with an *HNF1A* mutation is lower than that of people without the mutation, with increased insulin sensitivity in the former group (43). In the early phase of diabetes, these individuals are not dependent on exogenous insulin. When children with good metabolic control with low-dose insulin do not receive insulin, ketoacidosis is generally not observed (25).

In the early phases of the disease, an OGTT will show a marked increase in glucose (generally >90 mg/dL) at hour 2 (44). *HNF1A* has a role in glucose reabsorption via sodium glucose transporter-2 in the proximal renal tubules, meaning that glycosuria is observed in the period before the development of diabetes as a result of decreased renal glucose reabsorption in individuals carrying *HNF1A* mutations (45).

As severe hyperglycemia may be observed at the onset of diabetes, and the hyperglycemia severity increases over time, the risks of micro- and macrovascular complications in these patients are similar to those seen with T1DM and T2DM (46). Therefore, tight glycemic control and close follow-up for potential complications are necessary. It is believed that *HNF1A* mutations have no effect on the birth weight of children because in utero β-cell functions are normal (13).

HNF4A-MODY (MODY 1)

HNF4A, which is expressed mainly in the liver but also in the pancreas and kidneys, is a transcription factor that affects glucose metabolism through various pathways (47). *HNF4A* mutations constitute 10% of MODY cases, and more than 103 mutations have so far been defined in 173 families (34). The phenotype of heterozygote *HNF4A* mutations resembles that of *HNF1A*-MODY. In one study, 10–29% of individuals with suspected *HNF1A*-MODY were found to actually have *HNF4A* mutations, and the authors have suggested that sequencing of *HNF4A* should be performed in patients with clinical characteristics of *HNF1A*-MODY in whom mutations in *HNF1A* are not found (48).

Heterozygous mutations can cause significant fetal macrosomia (mean increase in body weight of 790 g) by increasing in utero insulin secretion, which can lead to transient or elongated neonatal hypoglycemia of unknown origin (49). The timing and cause of conversion from neonatal hyperinsulinemia to diabetes are unknown (1). Other differences between *HNF4A*-MODY and *HNF1A*-MODY are an absence of glycosuria and low apolipoproteins (apoAII, apoCIII, and apoB) in individuals with the former condition (50).

PDX1-MODY (MODY 4)

Pancreatic and duodenal homeobox 1 (encoded by *PDX1*), also known as insulin promoter factor 1 (*IPF1*), is a transcription factor that acts in pancreas development and gene transcriptions in the pancreas, including for insulin, glucose transporter-2, and glucokinase (51). Homozygote frameshift mutations or compound heterozygous mutations causing a premature stop codon can cause permanent neonatal diabetes as a result of pancreas agenesis (52). Heterozygous mutations of *PDX1* are related to MODY or early-onset T2DM development (53, 54). *PDX1*-MODY was first defined in 1997 and is a very rare cause of MODY (55). It was shown that the heterozygous Pro63fsX60 mutation, which was defined in five generations of a U.S. family, caused intermittent diabetes and MODY (56). The authors reported that the most noteworthy characteristics in these individuals were obesity before 12 years of age and hyperinsulinemia, and suggested that obesity might be observed in other types of MODY and was a general phenomenon of this condition (56). Individuals with *PDX1*-MODY should be followed up for cardiovascular complications and microvascular complications such as retinopathy and nephropathy, which are related to severe hyperglycemia (54–56).

HNF1B-MODY (MODY 5)

HNF1B is expressed in the early phase of embryonic development in the pancreas, kidneys, liver, and genital tract, and developmental abnormalities may therefore be encountered in all of these organs in individuals with *HNF1B* mutations (57). Renal diseases are most typically seen; the most commonly observed renal abnormality is renal cystic disease, followed by collecting-system abnormalities (58). Genitourinary abnormalities, pancreatic dysplasia, liver and gallbladder dysfunction, gout, and hyperuricemia are other accompanying problems (59, 60). To date, more than 65 heterozygous mutations have been reported in this gene, shown to cause MODY (58). Exon or complete gene deletion is observed in approximately half of individuals (58). Unlike the other MODY subtypes – such as *HNF1A*- and *HNF4A*-MODY—where the prominent feature is β-cell dysfunction, the diabetes that develops in approximately half of *HNF1B* mutation carriers is the result of both insulin resistance and β-cell dysfunction (26, 59). End-stage renal failure without diabetic nephropathy is observed at the age of 45 years in half of these individuals, and renal signs may be encountered before the appearance of diabetes (61); therefore, *HNF1B*-MODY should be considered in individuals with diabetic and non-diabetic nephropathy (42). Moreover, it has been reported that a family history might be absent in these individuals because spontaneous de novo mutations are encountered relatively frequently, and a positive family history should therefore not be required for molecular diagnosis (62).

Birth weights in heterozygous *HNF1B* individuals who developed early-adulthood diabetes have been reported to be approximately 900 g lower than normal (63). Individuals with *HNF1B*-MODY do not respond well to sulfonylureas, and they generally require early insulin therapy (26). Microvascular complications have also been reported in these patients (64, 65).

NEUROD1-MODY (MODY 6)

NEUROD1 is a regulating gene in the development of the pancreas and *INS* expression. It regulates *INS* expression by binding to a complex promoter that is formed after dimerization with protein E47 (66). It has been shown that heterozygous mutations of this gene – very rare mutations of which can result in permanent neonatal diabetes, cerebellar hypoplasia, and vision, hearing, and learning problems – might cause MODY in a small number of families (67, 68).

Individuals with *NEUROD1*-MODY may develop diabetes as children or adults (69). Another noteworthy feature of these individuals is that a majority are obese. It is not thought that obesity is related to *NEUROD1* mutations in these individuals but that obesity in mutation carriers might facilitate diabetes development (69, 70).

KLF11-MODY (MODY 7)

KLF11 is expressed in pancreatic islet cells and β-cells. Similar to expression in exocrine cells, *KLF11* mRNA expression in β-cells may be upregulated by transforming growth factor-β (40). In addition, high glucose levels increase *KLF11* mRNA expression in β-cells. It has been shown that in the presence of high glucose levels, *KLF11* can bind to and activate the insulin promoter in β-cells. These findings indicate that glucose-induced *KLF11* might increase insulin expression in pancreatic β-cells. Moreover, *KLF11* regulates *PDX1* transcription in pancreatic β-cells (71). Neve et al. (72) first defined two rare variants of the *KLF11* gene, which decreased its transcriptional activity, in three families with a history of early-onset T2DM.

CEL-MODY (MODY 8)

The *CEL* gene is mainly expressed in mammary glands and pancreatic acinar tissue, but it is not expressed in β-cells (73). The carboxyl ester lipase enzyme, which is known as a bile-salt-dependent/responsive lipase, is activated after it is secreted into the intestines by bile salts. It acts in the hydrolysis and absorption of cholesterol and fat-soluble vitamins. *CEL*-MODY was first defined by Raeder et al. (74) as an autosomal dominantly inherited disease, characterized by exocrine pancreatic dysfunction during the childhood and diabetes mellitus in adulthood. The pathogenesis of pancreatic lipomatosis and exocrine pancreatic dysfunction observed in the early phases of *CEL*-MODY is unknown (73).

PAX4-MODY (MODY 9)

Paired box gene 4 (encoded by *PAX4*) is a transcription factor that acts in β-cell development (75). *PAX4* is first expressed in endocrine promoter cells in the early phase of embryonic life and is then selectively expressed in β-cells later in life (76). *PAX4* is required for the expression of *PDX1* and Nkx 6.1, which are essential for the development

of pancreatic β-cells (75). Moreover, *PAX4* acts in regenerating β-cells in adulthood (14). A study looking at the *PAX4* gene in 46 individuals with MODY in the Far East determined that R164W and IVS7-1 G>A mutations were related to MODY (14).

INS-MODY (MODY 10)

While *INS* mutations generally cause neonatal diabetes, they are also rare causes of diabetes in older children and adults (77). A small number of heterozygous mutations showing co-segregation with diabetes and related to MODY have been defined (26). It has been predicted that these mutations decrease the folding of proinsulin molecules or cause stress and β-cell apoptosis in the endoplasmic reticulum via endoplasmic reticulum protein retention (77). Thus far, although the same mutations have been detected in individuals from the same family, clinical signs and diabetes severity have significantly varied among all individuals with *INS* gene mutations related to MODY (78, 79). In addition to individuals with polyuria, polydipsia, and weight loss, others with mild clinical signs have also been reported. Diabetes has been reported to develop after 50 years of age in family members of individuals who were diagnosed between 9 and 44 years, and carrying the same mutation (80). While some individuals can have good metabolic control for years with oral antidiabetes medication, others might require insulin treatment (79, 80).

BLK-MODY (MODY 11)

BLK encodes a nonreceptor tyrosine kinase of protooncogenes of the Src family, which act in cellular multiplication and differentiation, and are present in many cells and tissues, mainly in pancreatic β-cells (16). In addition, the *BLK* gene acts on insulin synthesis and secretion by increasing the expressions of *PDX1* and Nkx 6.1, which are essential for the development of pancreatic β-cells (16). Borowiec et al. (16) identified five different *BLK* mutations related to MODY in three families. In a recent study investigating the A71T mutation in 64 individuals with MODY of unknown cause, 4901 T2DM patients, and 4280 normoglycemic controls, this mutation was not detected in the MODY group but was detected in 52 subjects in the normoglycemic control group. It was also reported that this mutation might be weakly "diabetogenic" in the presence of obesity in the T2DM group (81).

ABCC8-MODY (MODY 12)

In a recent study including 85 patients with a similar phenotype to MODY1 or MODY3 but no mutations in *HNF1A* or *HNF4A*, it was reported that 8% (n=7) had mutations in the *ABCC8* gene (17).

KCNJ11-MODY (MODY 13)

In the literature, only 1 MODYX family is reported to have a p.Glu227Lys mutation in the *KCNJ11* gene (18).

Although more than 10 MODY-causing genes have been identified since the condition was first defined, the genetic cause is undetermined in 15–65% of individuals with MODY (MODYX).

Differential diagnosis and significance of a genetic diagnosis

A correct diagnosis and differentiating MODY from T1DM and T2DM are important when deciding on a patient's treatment and determining his or her prognosis, as well as detecting at-risk family members (31, 82, 83). A study conducted in the United Kingdom reported that patients experienced a delay of 13 years in receiving a MODY diagnosis from diabetes initiation (9). Furthermore, it has been estimated that approximately 80% of individuals with MODY are incorrectly diagnosed with T1DM and T2DM at presentation (9). A recent study conducted in the United States with children diagnosed with MODY by molecular methods reported that, before the genetic diagnosis, 36% received treatment for T1DM, 51% received treatment for T2DM, and 24% received treatment for MODY (sulfonylurea or anti-diabetes therapy) (11). This indicates that a diagnosis of MODY is seldom considered by many primary care physicians (7).

Pihoker et al. (11) reported that of 47 individuals with a MODY diagnosis (*GCK*, *HNF1A*, or *HNF4A*) confirmed by molecular methods, 44% presented with a complaint of weight loss, and 82% presented with polyuria and polydipsia, while 23% developed diabetic ketoacidosis with 6 months of diagnosis. Other studies have reported that the *HNF1A* mutation was identified by molecular methods in 5–10% of individuals who were diagnosed clinically with T1DM and who had a family history of diabetes and inconsistent signs of T1DM (absence of a high-risk tissue

group, autoantibody negativity, and/or a history of diabetes in three generations) (84–86). While anti-glutamic acid decarboxylase antibodies and/or anti-islet antigen 2 antibodies are detected in 87–94% of newly diagnosed T1DM patients, positivity of these antibodies has been reported to be similar to that of the normal population (<1%) in individuals with molecularly confirmed MODY (3, 87, 88). It should be noted that, in rare cases, T1DM and MODY can coexist in a single patient (89–91).

As the prevalence of T2DM in children increases, it is becoming more difficult to differentiate early-onset T2DM from MODY using the classic diagnostic features of MODY (i.e., age at onset and family history). It has been reported that one-third of individuals with *HNF1A*-MODY could not be differentiated from those with T2DM by this method (92). It is accepted that the absence of clinical signs such as obesity and the metabolic syndrome in patients with early-onset diabetes favors a diagnosis of MODY over T2DM (34). However, although it has been reported that obesity is typically rare in MODY individuals, the obesity epidemic among adolescents and young adults means that obesity is being more frequently reported in individuals with MODY. In one study conducted in the United Kingdom and France, 8–9% of individuals younger than 30 years with *HNF1A*-MODY who were referred for genetic analysis were obese (34). Similarly, although it was previously reported that the prevalence of acanthosis nigricans is very low among individuals with MODY, a recent study performed with pediatric-age MODY sufferers observed acanthosis nigricans in 40% of molecularly confirmed cases (11, 25). Therefore, in diabetic children who have non-obese first degree relatives with early onset diabetes and who are responsive to sulfonylureas, MODY should be considered and molecular analysis should be performed even in the presence of obesity and acanthosis nigricans (34). The clinical features of T1DM, T2DM, and MODY in children and adolescents are summarized in Table 2 (7, 21, 93).

Although MODY constitutes 1–2% of all diabetes cases, molecular confirmation of MODY is quite significant for the individual and his or her family. First, a correct diagnosis enables optimal treatment of the disease. In a patient who is being treated as having T1DM and receiving insulin therapy, switching to oral treatment (i.e., a sulfonylurea) after a diagnosis of *HNF1A*-MODY or *HNF4A*-MODY will not only improve the patient's quality of life but also result in marked improvements in glycemic control (82, 92). Second, molecular confirmation of MODY enables an estimate of the individual's prognosis. In an adolescent with mild hyperglycemia, a diagnosis of *GCK*-MODY, *HNF1A*-MODY, or T1DM will result in different strategies for treatment and follow-up (30, 46). Third, molecular confirmation may prompt the recognition of accompanying abnormalities, such as pancreatic and genitourinary abnormalities in individuals with *HNF1B*-MODY and exocrine pancreatic dysfunction in those with *CEL*-MODY (22). Finally, by diagnosing MODY, family members can be screened for carrier status and incorrect diagnoses prevented. It is recommended that all diabetic family members should undergo genetic screening, while unaffected family members should receive genetic counseling about the benefits and potential consequences of molecular diagnosis (13, 94). Figure 1 shows diagnostic and treatment algorithm for MODY.

Diagnosis of MODY

Direct sequencing can diagnose MODY with up to 100% sensitivity (13). Testing is often necessary for the following reasons: the clinical signs of MODY overlap with those of T1DM and T2DM, individuals diagnosed with MODY and T1DM are generally lean at the time of diagnosis; those with MODY do not generally require insulin treatment,

Table 2 Clinical features of T1DM, T2DM, and MODY in children and adolescents.

Feature	MODY	T1DM	T2DM
Age at diagnosis (generally) (years)	<25	5–20	>10
Patients with a family history of diabetes (%)	60–95	<10	90
Inheritance	Autosomal dominant	Polygenic	Polygenic
Obesity	Similar to general population	Similar to general population	Common
Insulin resistance /acanthosis nigricans/metabolic syndrome	Rare	Rare	Common
Polyuria, polydipsia	Variable	Common	Variable
Diabetic ketoacidosis	Rare	Common	Rare
Patients with β-cell antibodies (glutamic acid decarboxylase), %	<1	87–94	11–30
C-peptide levels	Normal	Undetermined	High-normal
Optimal treatment	Sulfonylurea (MODY 1, 3, 4)	Insulin	Metformin

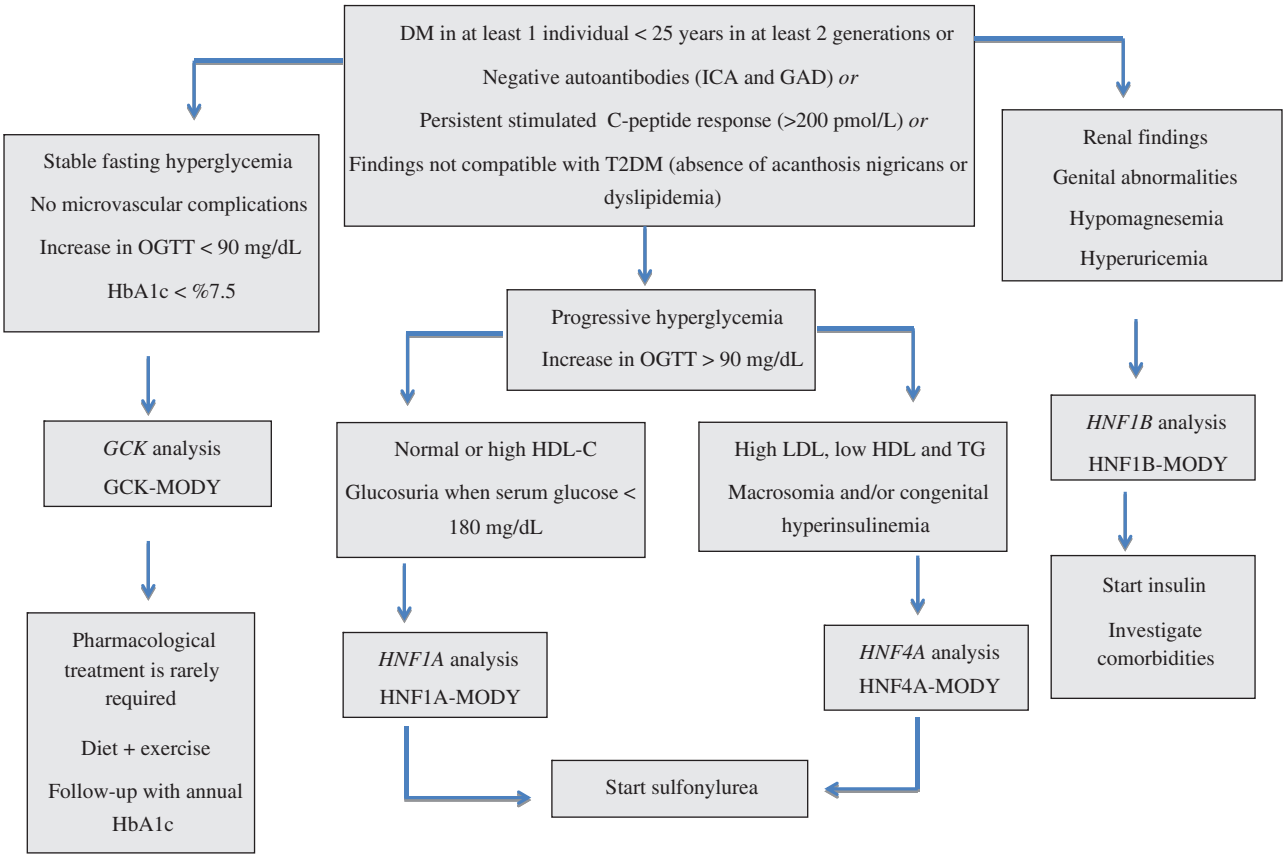

Figure 1 Diagnostic and treatment algorithm for MODY.

insulin secretion continues for a long time after diagnosis, and β-cell autoimmunity is absent. Moreover, it has been shown that the specificity of the typical diagnostic criteria (diagnosis at age <25 years, family history of diabetes, and absence of insulin dependence) is high but sensitivity is low, and fewer than half of individuals satisfy these criteria (9, 94). However, performing genetic tests in individuals without specific criteria can lead to inappropriate results and is not cost-effective, presenting a problem for the diagnosis of MODY.

Various algorithms using various clinical and laboratory parameters have been developed to define individual candidates for molecular diagnosis (12, 94). According to the model developed by Shields et al. (94), they reported that age younger than 30 years was the most differentiating feature between a diagnosis of MODY and T2DM and that the possibility of a MODY diagnosis was increased in previously diagnosed T1DM patients by 23-fold if there was family history of diabetes. This model uses age at the diagnosis, sex, treatment with insulin or an oral hypoglycemic agent, time to insulin treatment, body mass index, HbA_{1c} level, family history of diabetes, and current age of the individual to calculate the probability of MODY (94).

Thanabalasingham et al. (12) recommended molecular testing for all diabetic patients diagnosed before the age of 30 years with residual insulin secretion at least 3 years after diagnosis (i.e., a detectable C-peptide level), regardless of the patient's family history, autoimmune condition, and insulin resistance. They also showed that adding the presence of a C-peptide response and absence of the metabolic syndrome to the classic MODY criteria increased the diagnostic sensitivity by two-fold. In a study by Pihoker et al. (11) involving 586 children suspected of having MODY, mutations were identified in 47 individuals. Half of the children whose MODY diagnosis was confirmed by molecular methods did not have a parent with a history of diabetes. In addition, in a cohort from Slovakia and the Czech Republic, de novo mutations in *GCK*, *HNF1A*, or *HNF4A* were recently reported in 7.3% of MODY individuals without family history of diabetes and 1.2% of all individuals with MODY (95).

The expense of and difficulties in accessing molecular tests mean that many studies have been performed to determine nongenetic markers that might identify appropriate candidates for molecular investigation. An ideal marker should be cheap, easily accessible, and

differentiate between diseased and non-diseased individuals (i.e., be sensitive and specific). Because individuals with *HNF1A*-MODY have lower levels of high-sensitivity C-reactive protein (hs-CRP) than those with other types of diabetes (e.g., T1DM, T2DM, *GCK*-MODY), hs-CRP has been proposed as a marker in the differential diagnosis (96–98). Furthermore, it has recently been shown among adults with diabetes duration longer than 5 years that the urine C-peptide/creatinine ratio is higher in patients with *HNF1A*-MODY or *HNF4A*-MODY than in those with T1DM, with a sensitivity of 97% and specificity of 95% (99). The same investigators also found that this marker had a sensitivity of 100% and specificity of 97% in diagnosing non-T1DM (i.e., MODY or T2DM) among pediatric patients with a diabetes duration of 2 years; however, this marker was not useful in differentiating MODY from T2DM (100). Finally, a recent study conducted with adult individuals reported that a differential diagnosis between *GCK*-MODY and T1DM/T2DM might be made using HbA_{1c} levels (101).

Treatment

The treatment of individuals with *GCK*-MODY is not recommended because the hyperglycemia is mild and microvascular complications are not encountered (2). In addition, no change is observed in HbA_{1c} values after discontinuing treatment with insulin or oral hypoglycemic agents (30, 102). The exception is pregnant women, in whom insulin may be required to prevent fetal overgrowth. The recommendations for insulin therapy in pregnancy differ between centers, with some starting treatment immediately and others only instituting therapy if there is fetal overgrowth (103). Higher-than-standard doses of insulin may be required for pregnant women (104).

Sulfonylureas have been shown to be effective in treating individuals with *HNF1A*-MODY by acting on ATP-sensitive potassium channels (13). It has also been reported that gliclazide improved fasting blood glucose levels by 5.2-fold compared with metformin and that patients with *HNF1A*-MODY are more sensitive to insulin (82). The same study determined that the mean duration of diabetes in patients with *HNF1A*-MODY is 18 years (82), and other studies have reported that switching from insulin to gliclazide is effective and safe in individuals receiving long-term insulin treatment (83, 105). In an observational study in which 80% of *HNF1A*-MODY patients who had received insulin for a mean duration of 4 years were switched to gliclazide, all of the patients had perfect glycemic control (mean HbA_{1c} 6.9%) during the 39 months of follow-up (83). Moreover, it has been shown that the postprandial secretagogue nateglinide is associated with a lower insulin peak and fewer hypoglycemic episodes, with more effective postprandial blood glucose control, when compared with glibenclamide (106). Case reports have indicated that meglitinides and glucagon-like peptide-1 agonist therapy are also effective in treating patients with *HNF1A*-MODY (107, 108). Patients with *HNF1A*-MODY experience an approximately 1–4% decrease in insulin secretion each year, which is induced by glucose as the result of progressive β-cell damage (105). A low-dose sulfonylurea (e.g., 20–40 mg/day gliclazide) is the preferred long-term treatment. In general, patients with *HNF1A*-MODY develop sulfonylurea unresponsiveness after 3–25 years due to the progressive decrease in insulin secretion and become insulin dependent in adulthood (105). Similar response to sulfonylureas has been reported in patients with *HNF4A*-MODY (48).

Patients with *HNF1B*-MODY do not generally respond to sulfonylureas and typically require insulin early on in their disease. Moreover, these patients have been reported to develop microvascular complications (64, 65).

As mutations in other genes are rare, there is insufficient information about the phenotypical characteristics of patients and the clinical progression of diabetes to recommend specific treatments.

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