

Review

Diagnosis and Treatment of MODY: An Updated Mini Review

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Abstract: Maturity-Onset Diabetes of the Young (MODY) is the most common form of monogenic diabetes resulting from a single gene mutation. It is characterized by mild hyperglycemia, autosomal dominant inheritance, early onset of diabetes (<25 years), insulin resistance, and preservation of endogenous insulin secretion. Currently, 14 MODY subtypes have been identified, with differences in incidence, clinical features, diabetes severity and related complications, and treatment response. This type of diabetes is mostly misdiagnosed as either type 1 or type 2 diabetes mellitus because it is difficult to differentiate between these forms of diabetes due to clinical similarities, the high cost of genetic testing, and lack of awareness. As a result, thousands of patients are not receiving appropriate treatment. Accurate diagnosis would allow for more effective therapeutic management and treatment strategies that are distinct from those used for type 1 and type 2 diabetes. This review serves to explore MODY subtypes, diagnosis, and treatment, and increase awareness of MODY incidence.

Keywords: maturity onset diabetes of the young; diabetes; genetic testing; gene mutations; *HNF1A*; glucokinase (*GCK*)



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1. Introduction

Maturity-Onset Diabetes of the Young (MODY) is a monogenic type of diabetes, resultant from single gene mutations [1]. MODY is characterized by mild hyperglycemia, autosomal dominant inheritance, early onset of diabetes (<25 years), insulin resistance, and preservation of endogenous insulin secretion [2–4]. The genes involved are crucial for the development, function and regulation of beta cells and can cause glucose sensing and insulin secretion disorders [5,6]. MODY is classified into several subtypes based on the genes involved and clinical phenotypes. Fourteen MODY subtypes have been identified thus far, each caused by a distinct gene mutation (Table 1) [7]. Among the 14 MODY subtypes, mutations in hepatocyte nuclear factor 1- α (*HNF1A*), glucokinase (*GCK*), *HNF4A*, and *HNF1B* are the underlying cause in more than 95% of MODY cases; the other mutations are uncommon in the Caucasian population [2,8–10]. These mutations differ in terms of prevalence, clinical features, the severity of diabetes and related complications, and treatment response. Each mutation encodes proteins involved in glucose homeostasis of pancreatic β -cells [11,12].

2. Diagnosis of MODY

Misdiagnosis of MODY with type 1 (T1DM) or type 2 diabetes mellitus (T2DM) can be avoided if clinicians can establish a correct molecular diagnosis, and with advances in genetic testing, aided by the development of new techniques (e.g., Next Generation Sequencing) and increased access to genetic testing facilities, diagnosis of MODY can be performed accurately [13]. However, in order to ensure an accurate diagnosis, specific criteria must be met before administering genetic tests [2]. MODY can be distinguished from other types of diabetes based on the age at which the disease first manifested. MODY

subtypes with variable age of onset, low penetrance, or atypical presentation may fail to meet the diagnostic criteria for the disease [14–17]. Additionally, while a family history of diabetes is highly suggestive of MODY, some mutations in MODY-associated genes can occur at high frequencies in individuals without a family history of diabetes, demonstrating the critical nature of genetic testing in individuals without a family history of diabetes [18]. According to the MODY diagnostic guidelines, genetic testing should be performed on individuals diagnosed with diabetes at a young age (25 years), as well as those with a familial history of diabetes, evidence of endogenous insulin secretion, detectable levels of c-peptide, and negative antibody results [19]. Direct sequencing with sensitivity close to 100% and next generation sequencing methods can be successfully used to identify MODY gene mutations [1,9,20]. According to a model proposed by Shields et al., a diagnosis before the age of 30 years is a useful discriminator between MODY and T2DM, whereas a parental history of diabetes produces a 23-fold increased chance that a patient previously diagnosed with T1DM may be diagnosed with MODY at a later stage [9].

Table 1. Summary of MODY subtypes, gene names, locus, and their clinical features.

Type	Gene Name	Locus	Clinical Features	Reference
1	<i>HNF4A</i>	20q13.12	Mild - increased fasting and postprandial plasma glucose, sensitivity to sulfonylurea derivatives, low levels of apolipoproteins and triglycerides, neonatal macrosomia, neonatal hypoglycemic events	[11,21]
2	<i>GCK</i>	7p13	Mild fasting hyperglycemia, impaired fasting glucose and impaired glucose tolerance, HbA1c is usually 7.3–7.5%	[11,22,23]
3	<i>HNF1A</i>	12q24.31	Diminished renal threshold for glycosuria, sensitivity to sulfonylurea derivatives, transient neonatal hyperinsulinemic hypoglycemia	[24]
4	<i>IPF/PDX1</i>	13q12.2	Pancreatic agenesis, permanent neonatal diabetes in homozygote	[9,25]
5	<i>HNF1B</i>	17q12	Characterized by renal disease and urogenital tract abnormalities in females, exocrine pancreatic dysfunction, hyperuricemia	[2,25]
6	<i>NEUROD1</i>	2q31.3	Characterized by obesity and insulin resistance, neonatal diabetes, child or adult-onset diabetes neurological abnormalities	[26,27]
7	<i>KLF11</i>	2p25.1	Pancreatic malignancy	[26]
8	<i>CEL</i>	9q34.13	Associated with both endocrine and exocrine pancreatic dysfunction, lipomatosis and fibrosis	[25,26]
9	<i>PAX4</i>	7q32.1	Important for transcription for beta cell development	[26]
10	<i>INS</i>	11p15.5	Associated with neonatal diabetes	[2]
11	<i>BLK</i>	8p23.1	Contributes to control of beta signaling	[2]
12	<i>ABCC8</i>	11p15.1	Associated with renal diabetes	[2]
13	<i>KCNJ11</i>	11p15.1	Associated with renal diabetes	[2]
14	<i>APPL1</i>	3p14.3	Associated with Wolfram or DIDMOAD syndrome	[2]

GCK: Glucokinase, *HNF1A*, *HNF4A*, *HNF1B*: Hepatic nuclear factor alpha/beta, *PDX1/IPF1*: Pancreatic and duodenal homeobox 1/Insulin promoter factor 1, *NEUROD1*: Neurogenic differentiation factor 1, *KLF11*: Krueppel-like factor 11, *CEL*: Carboxyl ester lipase, *PAX4*: Paired Box 4, *INS*: Insulin, *BLK*: *BLK* proto-oncogenes, Src family tyrosine kinase, *ABCC8*: ATP binding cassette subfamily C member 8, *KCNJ11*: Potassium voltage-gated channel subfamily J member 11, *APPL1*: Adaptor protein, phosphotyrosine interacting with PH domain and leucine Zipper 1, DIDMOAD: Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.

3. Significance of MODY Diagnosis

Although MODY accounts for only 1–5% of all diabetes cases, it has significant implications [28]. The diagnosis of MODY is crucial for patients and their families; therefore, it is important to characterize each MODY subtype and distinguish these from other types

of diabetes. MODY patients are often misdiagnosed with either T1DM or T2DM, resulting in patients receiving inappropriate treatment [26]. This could be due to overlapping clinical features, which are more common in diabetes, the high cost of genetic testing, and clinicians' lack of awareness [29]. Accurate diagnosis would enable optimal therapeutic management and treatment strategies that differ significantly from those used for T1DM or T2DM [7]. Patients who had been receiving T1DM treatment can switch to oral agents (i.e., sulfonylureas), which will improve their quality of life and glycemic control [30]. For example, *HNF1A*-MODY (MODY 3) and *HNF4A*-MODY (MODY 1) patients are best managed with oral sulfonylureas and can avoid the unnecessary insulin therapy that is generally prescribed before MODY diagnosis [31]. MODY diagnosis is key to providing accurate counselling regarding the predicted clinical outcome, genetic counselling, and identification of affected family members [32].

4. MODY Subtypes and Their Treatments

4.1. *HNF4A*-MODY (MODY 1)

MODY 1 is caused by a mutation in the hepatocyte nuclear factor 4A (*HNF4A*) gene, which is expressed primarily in the liver, but also in the pancreas and kidney. The *HNF4A* gene regulates the expression of genes involved in lipid metabolism and hepatic gluconeogenesis [2,33,34]. The mutations in this gene result in decreased insulin production, which is linked to autosomal dominant non-insulin T1DM [35]. Heterozygous mutations in this gene result in beta cell dysfunction, impaired glucose-stimulated insulin secretion, elevated low-density lipoprotein (LDL), and low levels of high-density lipoprotein (HDL) and triglycerides [35]. Affected individuals may present with fetal macrosomia, transient neonatal hyperinsulinemic hypoglycemia, progressive development of hyperglycemia, and the onset of diabetes mellitus in late adolescence or by the age of 25 years [24]. During the first decade of life, MODY 1 patients present with normal glucose tolerance [34]. At the time of diagnosis and in the early stages of the disease, patients with MODY1 can control their glycemia solely through diet, though both have elevated postprandial glucose levels after eating carbohydrate-rich foods [36]. However, most patients' β -cell function will deteriorate over time, necessitating pharmacological treatment [27]. Individuals with *HNF4A*-MODY are sensitive to sulfonylureas [27] and are best treated with low-dose sulfonylureas rather than insulin (Table 2) [30,37–39], due to an increased insulin secretory response in the pancreas to sulfonylureas and increased insulin sensitivity to secreted insulin [30]. However, in advanced disease or during pregnancy, insulin therapy is usually required [34].

Table 2. Summaries of MODY subtypes and treatments.

Gene Name	Pathophysiology	Treatment
<i>HNF4A</i>	β -cell dysfunction	Sulfonylureas, Insulin
<i>GCK</i>	Glucose-sensing defects, β -cell dysfunction	Diet, except possibly during pregnancy
<i>HNF1A</i>	β -cell dysfunction	Sulfonylureas
<i>IPF/PDX1</i>	β -cell dysfunction	Insulin or Diet
<i>HNF1B</i>	β -cell dysfunction	Insulin
<i>NEUROD1</i>	β -cell dysfunction	OAD or Insulin
<i>KLF11</i>	Decreased glucose sensitivity of β -cells	OAD or Insulin
<i>CEL</i>	Pancreatic endocrine and exocrine dysfunction	OAD or Insulin
<i>PAX4</i>	β -cell dysfunction	Diet, OAD, or Insulin
<i>INS</i>	β -cell dysfunction, insulin gene mutation	OAD OR Insulin
<i>BLK</i>	β -cell dysfunction, affected insulin secretion	Diet, OAD, or Insulin
<i>ABCC8</i>	Insulin secretion defects, ATP-sensitive potassium channel dysfunction	Diet, Insulin, Sulfonylureas
<i>KCNJ11</i>	ATP-sensitive potassium channel dysfunction	Sulfonylureas
<i>APPL1</i>	Insulin secretion defects, development delay	OAD or Insulin

OAD: Oral anti-diabetes drug.

4.2. GCK-MODY (MODY 2)

Glucokinase (GCK), also known as Hexokinase IV or D, belongs to the hexokinase family, and is one of the most common forms of MODY. The GCK gene plays a significant role in glucose-stimulated insulin secretion in the pancreas, while it contributes to glucose uptake and glycogen conversion in the liver [40,41]. GCK gene mutations result in MODY 2 [41,42] and have been shown to cause abnormal glucose sensing, resulting in a higher threshold for glucose-stimulated insulin secretion initiation. HbA1c levels are typically less than 7.3–7.5% [22,23]. The vast majority of MODY 2 patients have slightly elevated fasting plasma glucose levels but no postprandial hyperglycemia, meaning they produce enough insulin in response to a rise in blood glucose levels after eating [27]. GCK-MODY treatment is usually unnecessary; patients with confirmed GCK-MODY do not need treatment other than dietary alterations, because their long-term outcomes are comparable to those of healthy individuals [40,43,44]. However, insulin should be administered during pregnancy to reduce the risk of fetal macrosomia [45]. Although the fetal genotype is not always known, serial ultrasound measurements may be used to determine growth. If no evidence of accelerated growth is found, the fetus is assumed to have inherited the GCK mutation, and maternal hyperglycemia is not treated [46].

4.3. HNF1A-MODY (MODY 3)

MODY 3 is a common MODY type and is caused by *HNF1A* gene mutations [40]. The *HNF1A* gene is found in the liver, kidney, intestine, and pancreatic β -cells and it has been shown to control the expression of insulin genes in mature β -cells as well as the glucose transport *GLUT2* genes [7,47,48]. Mutations in the *HNF1A* gene can cause impaired dimerization, resulting in a malfunction of the molecular mechanisms and diabetes mellitus. *HNF1A*-MODY displays a glycemic pattern that includes mild fasting hyperglycemia and extremely high glucose levels after glucose administration [34]. *HNF1A*-MODY is characterized by transient neonatal hyperinsulinemic hypoglycemia, progressive hyperglycemia throughout childhood, and the onset of diabetes mellitus by the age of 25 years [24]. Insulin secretion gradually decreases in patients with *HNF1A*-MODY, with glucose control deteriorating over time and necessitating treatment. Furthermore, 63% of patients develop diabetes before the age of 25, 79% before the age of 35, and 96% before the age of 55 [34,37]. Individuals with *HNF1A*-MODY are treated based on their age and HbA1c levels [49]. At first, *HNF1A*-MODY is treated with a low-dose diet and sulfonylureas, but insulin administration is required at later disease stages or during pregnancy [34,50,51]. Glucagon-like peptide-1 receptor agonists (GLP-1 Ras) have been shown to effectively manage *HNF1A*-MODY, which was validated in a clinical trial [52–55].

4.4. PDX1-MODY (MODY 4)

The pancreatic and duodenal homeobox 1 (*PDX1*) gene is a homeodomain-containing transcriptional factor, which regulates insulin gene expression and pancreatic development [40,56,57]. *PDX1*-MODY is a rare type of MODY caused by heterozygous mutations in the *PDX1* gene. It is important in the regulation of genes that code for glucagon, insulin, glucose transporter 2 (*GLUT2*), and glucokinase (*GCK*) enzymes [58]. It acts as the master switch for the pancreas' hormonal and enzymatic functions [59]. Heterozygous *PDX1* mutations can result in defective insulin secretion, whereas homozygous mutations result in permanent neonatal diabetes (PND) and exocrine pancreatic insufficiency [56,60,61]. Patients with *PDX1*-MODY present with type 2 diabetes with early onset and no extra-pancreatic involvement. Metformin [62] and dipeptidyl peptidase-4 (DPP-4) inhibitors [63] have been shown to be effective in case reports. Diet, oral anti-diabetes drugs (OADs), and insulin are all options to treat individuals with MODY 4 [34,51].

4.5. HNF1B-MODY (MODY 5)

MODY 5 is a rare type of the disease caused by hepatocyte nuclear factor 1B (*HNF1B*) gene mutations [40]. *HNF1B* is a transcription factor of the homeodomain-containing tran-

scription factor superfamily and is found in a wide range of tissues, such as liver, intestine, stomach, lung, and pancreas [34,40,64]. It is involved in many developmental processes, including the development of the nephron and the embryonic pancreas [65,66]. Patients with *HNF1B*-MODY often have significant histological abnormalities, such as renal cysts and diabetes (RCAD) syndrome. *HNF1B*-MODY has variable multisystemic phenotypes with a wide range of pancreatic and extrapancreatic clinical manifestations [34,67,68]. Severe kidney disease results from mutations in this gene, which can appear before glucose tolerance is impaired [69]. MODY 5 can cause complications like vaginal aplasia, a rudimentary uterus, hyperglycemia, gout, and a reduction in infant birth weight (900 g) [66,70,71]. *HNF1B*-MODY patients exhibit hepatic insulin resistance [30], sulfonylurea therapy is inefficient, and early insulin administration may be necessary [72].

4.6. *NEUROD1*-MODY (MODY 6)

Neurogenic differentiation 1 (*NEUROD1*), a transcription factor with a basic-loop-helix structure that is expressed in neuronal and pancreatic cells, is essential for pancreatic and neuronal development, influencing pancreatic morphology and neuronal differentiation [65,73]. *NEUROD1* plays a role in insulin transcription activation by binding to and activating the promoters of sulfonyl-urea receptor 1 (*SUR1*), *GCK*, and *PAX6* (glucose-6-phosphatase catalytic subunit-related protein) [34,74]. Mutations in the *NEUROD1* gene result in MODY 6 [40]. Heterozygous mutations in the *NEUROD1* gene result in beta cell dysfunction [73]. Insulin therapy is a common treatment option, but MODY 6 patients present with diabetes with incomplete penetrance; thus, half of MODY 6 patients appear to benefit from OADs and diet management [75].

4.7. *KLF11*-MODY (MODY 7)

Krueppel-like factor 11 (*KLF11*)-MODY occurs as a result of heterozygous *KLF11* gene mutations. The *KLF11* gene encodes for a transcriptional factor from the KLF/Sp1 family found in all human tissues [40,76]. *KLF11* regulates the expression of free radical scavengers, such as catalase and superoxide dismutase (SOD), both of which are essential for pancreatic β -cell function (SOD) [40,65,77]. Heterozygous mutations in the *KLF11* gene eventually result in beta cell dysfunction and insulin secretion impairment [76]. *KLF11*-MODY is a type of diabetes that appears early in life and is treated with either OADs or insulin [34,50].

4.8. *CEL*-MODY (MODY 8)

MODY 8 is caused by mutations in the carboxyl ester lipase (*CEL*) gene, which regulates the exocrine and endocrine functions of the pancreas. It is commonly found in the mammary glands and acinar tissue of the pancreas [40,78,79]. *CEL* is important in infants, because it aids in milk digestion and the hydrolysis of dietary esters in the duodenum [80]. Heterozygous mutations in the *CEL* gene are linked to early pancreatic atrophy and subsequent exocrine insufficiency, pancreatic lipomatosis, and endocrine dysfunction caused by carboxyl-ester lipase misfolding and cytotoxic aggregation [78,79,81,82]. *CEL* MODY manifests as diabetes mellitus in adulthood [50]. Insulin appears to be the most appropriate treatment for MODY 8; however, OADs can also be used [34,79,81].

4.9. *PAX4*-MODY (MODY 9)

MODY 9 is caused by heterozygous mutations in the paired box 4 (*PAX4*) gene, which encodes for a transcription factor that is required for insulin-producing beta-cell generation, differentiation, development, and survival [34,40]. During the early stages of embryonic development, *PAX4* is expressed in endocrine promoter cells, and later in β -cells [83]. Ketosis-prone diabetes has been associated with mutations in *PAX4* gene [84]. At the early stages, MODY 9 patients are treated with dietary changes or OADs [85]. However, at more advanced stages of disease, affected patients may require insulin administration [86].

4.10. *INS-MODY (MODY 10)*

The insulin (*INS*) gene encodes for pro-insulin, and its mutation can result in primary defects in nuclear factor Kappa-light-chain-enhancer of activated B cells (NF- κ B) [40,87]. Heterozygous gene mutations in the *INS* gene results in MODY 10, which is characterized by decreased beta cell mass, gradual loss of insulin secretion, and variable-onset diabetes mellitus. Although dominant misfolding mutations in the *INS* gene are a frequent cause of isolated permanent neonatal diabetes, the onset age of the disease varies [88]. These mutations result in a severe folding defect, an abnormal response to unfolded proteins, and β -cell apoptosis [89]. During the time of diagnosis, diet or OADs may be used as treatment for patients with MODY, but they eventually become insulin dependent [88,90].

4.11. *BLK-MODY (MODY 11)*

MODY 11 is caused by heterozygous tyrosine-protein kinase (*BLK*) gene mutations. The *BLK* gene, which belongs to the SRC proto-oncogenes family, encodes a tyrosine receptor protein that stimulates β -cells to produce and secrete insulin [40]. The *BLK* gene is expressed in β -cells and is essential for thymopoiesis in immature T cells [91]. *BLK*-MODY has incomplete penetrance, and as a result not all carriers present with diabetes. Heterozygous mutations in this gene reduce BLK expression and/or activity, leading to PDX1 and NKX6.1 deficiency, impaired glucose-stimulated insulin secretion, and decreased beta cell mass [92]. Environmental and genetic factors are thought to play a role in *BLK*-MODY, and the most important factor that causes hyperglycemia is excessive body weight [93]. Hyperglycemia is also likely to be influenced by pregnancy [94]. Although insulin is required for the vast majority of patients, some may be treated with diet or OADs [34,50].

4.12. *ABCC8-MODY (MODY 12)*

MODY 12 is caused by heterozygous ATP binding cassette subfamily C member 8 (*ABCC8*) gene mutations. *ABCC8* encodes for sulfonyl-urea receptor 1 (SUR1), a subunit of an ATP-sensitive potassium (K-ATP) channel found in β -cell membranes [40,65]. *ABCC8* is responsible for the secretion of insulin, which controls blood sugar levels [95]. *ABCC8* gene mutations can result in congenital hyperinsulinism, which can be caused by dominantly inherited inactivating mutations. As a result of activating mutations or recessive loss-of-function mutations, *ABCC8* gene mutations can lead to permanent or transient neonatal diabetes (PNDM or TNDM, respectively) [95]. The majority of patients with MODY 12 are misdiagnosed as having diabetes of a different kind and are mistreated with insulin, resulting in poor control and hypoglycemia episodes [34]. Rafiq et al. proposed that in adulthood, all *ABCC8* mutation carriers could be switched to sulfonylureas [96].

4.13. *KCNJ11-MODY (MODY 13)*

MODY 13 is caused by heterozygous mutations in the potassium inwardly rectifying channel subfamily J member 11 (*KCNJ11*) gene, which encodes for human BIR (beta cell inward rectifier) and Kir6.2, subunits of K-ATP channels [7,97,98]. This gene mutation causes severe conditions, such as channel inactivation due to disrupted subunit interaction. This disruption was discovered to be linked to Arg301 mutations, which typically result in hyperinsulinism and possibly neonatal diabetes [65,99]. *KCNJ11*-MODY is best treated with high-dose sulfonylureas for extended periods of time [34,50,100].

4.14. *APPL1-MODY (MODY 14)*

MODY 14 is a rare subtype caused by mutations in the adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (*APPL1*) gene, which regulates cell proliferation and interaction between the adiponectin and insulin signaling pathways [101,102]. Heterozygous loss-of-function mutations in this gene result in impaired insulin secretion in response to glucose stimulation and decreased beta cell survival [101–103]. *APPL1* mutations can cause apoptosis in highly expressed tissues; overexpression causes dysmorphic

phenotypes and developmental delays [101]. Diet, OADs, and insulin are all possible *APPL1*-MODY treatments [34,50].

5. Conclusions

MODY is a rare type of diabetes that is difficult to diagnose, resulting in frequently misdiagnosed patients. As a result, these patients often receive ineffective treatment, which can aggravate disease complications. Molecular diagnosis is critical in determining the best treatment for the majority of patients with MODY; therefore, clinicians should be familiar with the pathogenesis and various biomarkers for MODY because this information is crucial for accurate diagnosis, individualized patient management, and family screening.

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