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Maturity-Onset Diabetes of the Young: What Do Clinicians Need to Know?

Sung-Hoon Kim

Division of Endocrinology & Metabolism, Department of Medicine, Cheil General Hospital & Women's Healthcare Center, Dankook University College of Medicine, Seoul, Korea

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes that is characterized by an early onset, autosomal dominant mode of inheritance and a primary defect in pancreatic β-cell function. MODY represents less than 2% of all diabetes cases and is commonly misdiagnosed as type 1 or type 2 diabetes mellitus. At least 13 MODY subtypes with distinct genetic etiologies have been identified to date. A correct genetic diagnosis is important as it often leads to personalized treatment for those with diabetes and enables predictive genetic testing for their asymptomatic relatives. Next-generation sequencing may provide an efficient method for screening mutations in this form of diabetes as well as identifying new MODY genes. In this review, I discuss a current update on MODY in the literatures and cover the studies that have been performed in Korea.

Keywords: Diagnosis; Maturity-onset diabetes of the young; Personalized treatment

INTRODUCTION

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes that is characterized by an early onset, autosomal dominant mode of inheritance and a primary defect in pancreatic β-cell function. In 1974, it was first described by Tattersall [1] with a mild form of diabetes in three families who had a dominant mode of inheritance. In the 1990s, advances in molecular genetics and the availability of large pedigrees aided in the identification of genes that are responsible for this form of diabetes. MODY has been well characterized in European and North American populations. MODY is a common form of monogenic diabetes and it may account for 1% to 2% of all diabetes cases in Europe [2]. Although MODY has been identified in Asian populations, the prevalence is not known. In this review, I summarize a current update of MODY and cover the studies that have been conducted in Korean MODY subjects.

CLASSIFICATION OF MODY AND PHENOTYPIC CHARACTERISTICS

Genetic heterogeneity of MODY

Even though MODY is well known as a monogenic disorder, it is not a single entity but represents genetic, metabolic, and clinical heterogeneity [3]. Genes that are known to cause MODY are: hepatocyte nuclear factor 4 α (HNF4A; MODY1), glucokinase (GCK; MODY2), HNF1A (MODY3), pancreatic and duodenal homeobox 1 (PDX1; MODY4), transcription factor 2 (TCF2) or HNF1B (MODY5), neurogenic differentiation 1 (NEUROD1; MODY6), Kruppel-like factor 11 (KLF11; MODY 7), carboxyl ester lipase (CEL; MODY8), paired-box-containing gene 4 (PAX4; MODY9), insulin (INS; MODY10), B-lymphocyte kinase (BLK; MODY11), adenosine triphosphate (ATP)-binding cassette, sub-family C (CFTR/MRP), member 8 (ABCC8; MODY12), and potassium channel, inwardly rectify-

Corresponding author: Sung-Hoon Kim
Division of Endocrinology & Metabolism, Department of Medicine, Cheil General Hospital & Women's Healthcare Center, Dankook University College of Medicine, 17 Seoae-ro 1-gil, Jung-gu, Seoul 04619, Korea
E-mail: hoonie.kim@cgh.co.kr
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ing subfamily J, member 11 (KCNJ 11; MODY13). The 13 MODY genes thus far identified do not account for all cases of MODY; thus, additional genes responsible for MODY exist and remain to be identified.

Mutations in the GCK, HNF1A, HNF4A, and HNF1B genes are the most common causes of MODY, and they respectively account for 32%, 52%, 10%, and 6% of cases in the UK [4]. However, the disease-causing mutations in Asian and Caucasian MODY patients are different. In Korea, only 10% of 40 MODY or early onset type 2 diabetes mellitus (T2DM) patients had known MODY gene defects (HNF1A 5%, GCK 2.5%, and HNF1B 2.5%) among MODY 1-6 genes [5,6]. Only 10% to 20% of MODY cases are caused by Known MODY genes in Japan and China [7,8]. So, more MODY genes should be discovered in Asian countries. Genes causing MODY and their clinical and molecular characteristics are summarized in Table 1.

MODY subtypes and their clinical characteristics

***GCK-MODY* (*MODY2*)**

GCK is a glycolytic enzyme that catalyzes the conversion of glucose to glucose-6-phosphate and is referred to as the β-cell glucose sensor because it controls glucose-mediated insulin release. Heterozygous inactivating mutations in GCK cause GCK-MODY, also known as MODY2, which was first recognized in 1992 [9]. A total of 620 mutations in 1,441 families have been identified so far to cause hypoglycemia and hyperglycemia [10]. GCK mutations have been reported throughout the world. In one study of Japanese patients with pediatric-onset MODY-type diabetes, GCK-MODY was reportedly the most common form (approximately 48%) [11]. This proportion was similar to a report in European population [12]. However, only a small proportion (<5%) of MODY cases were caused by GCK-MODY in Korea and China [6,8].

The clinical disease manifests as mild fasting hyperglycemia

Table 1. Clinical and molecular characteristics of MODY subtypes

MODY gene	Chromosomal location	Frequency (% from MODYs)	Pathophysiology	Other features	Treatment
HNF4A	20q13	5	β-Cell dysfunction	Neonatal hyperinsulinemia, low triglycerides	Sensitive to sulfonylurea
GCK	7p13	15–20	β-Cell dysfunction (glucose sensing defect)	Fasting hyperglycemia from newborn	Diet
HNF1A	12q24	30–50	β-Cell dysfunction	Glycosuria	Sensitive to sulfonylurea
PDX1/IPF1	13q12	<1	β-Cell dysfunction	Homozygote: pancreatic agenesis	Diet or OAD or insulin
HNF1B	17q12	5	β-Cell dysfunction	Renal anomalies, genital anomalies, pancreatic hypoplasia	insulin
NEUROD1	2q31	<1	β-Cell dysfunction	Adult onset diabetes	OAD or insulin
KLF11	2p25	<1	β-Cell dysfunction	Similar to type 2 diabetes mellitus	OAD or insulin
CEL	9q34	<1	Pancreas endocrine and exocrine dysfunction	Exocrine insufficiency, lipomatosis	OAD or insulin
PAX4	7q32	<1	β-Cell dysfunction	Possible ketoacidosis	Diet or OAD or insulin
INS	11p15	<1	Insulin gene mutation	Can also present PNDM	OAD or insulin
BLK	8p23	<1	Insulin secretion defect	Overweight, relative insulin secretion defect	Diet or OAD or insulin
ABCC8	11p15	<1	ATP-sensitive potassium channel dysfunction	Homozygote: permanent neonatal diabetes; heterozygote: transient neonatal diabetes	OAD (sulfonylurea)
KCNJ11	11p15	<1	ATP-sensitive potassium channel dysfunction	Homozygote: neonatal diabetes	Diet or OAD or insulin

MODY, maturity-onset diabetes of the young; HNF4A, hepatocyte nuclear factor 4 α; GCK, glucokinase; PDX1, pancreatic and duodenal homeobox 1; IPF1, insulin promoter factor 1; OAD, oral antidiabetic agents; NEUROD1, neurogenic differentiation 1; KLF11, Kruppel-like factor 11; CEL, carboxyl ester lipase; PAX4, paired-box-containing gene 4; INS, insulin; PNDM, permanent neonatal diabetes; BLK, B-lymphocyte kinase; ABCC8, ATP-binding cassette, subfamily C (CFTR/MRP), member 8; ATP, adenosine triphosphate; KCNJ11, potassium channel, inwardly rectifying subfamily J, member 11.

(5.5 to 8.0 mmol/L, glycosylated hemoglobin range 5.8% to 7.6%) from birth that demonstrates slight deterioration with age. Patients are usually asymptomatic, so many are first discovered during routine screening such as during pregnancy. Severe hyperglycemia and microvascular complications are rare in GCK diabetes [13]. Clinical features of the Japanese patients with GCK-MODY were similar to those that had been previously reported for Caucasians, although 25% of patients demonstrated signs of insulin resistance [14].

Patients with GCK-MODY do not require treatment outside pregnancy because glucose-lowering therapy is ineffective and there is a lack of long-term complications [15]. In pregnancy, insulin may be required to prevent fetal overgrowth. The fetal growth in pregnancy is dependent on whether the mutation is inherited [16]. Management of pregnant women with GCK-MODY is based on fetal growth scans which are surrogates for fetal genotype.

HNF1A-MODY (*MODY3*)

HNF1A is a homeodomain-containing transcription factor, which is expressed in the liver, kidney, intestine, and pancreatic β-cells. *Hnf1a*-knockout mice developed diabetes because of impaired glucose-induced insulin secretion [17]. Mutations in HNF1A are the most common cause of MODY in Europe, North America, and Asia [18]. In Asia, 5% to 20% of MODY cases are caused by HNF1A mutations. A total of 414 different HNF1A mutations in 1,247 families have been discovered [19]. Although mutations are located throughout the minimal promoter, exons and flanking intronic regions, they are more often detected in exons 2 and 4. A novel missense mutation (R263L) of HNF1A was found in a Korean MODY family and reportedly caused diabetes through defective glucose sensing and insulin secretion [20].

Heterozygous HNF1A mutations result in progressive β-cell dysfunction that leads to diabetes in early adult life. These mutations demonstrate high penetrance; 63% of carriers develop diabetes by 25 years of age, and almost all carriers develop diabetes by the age of 55 [21]. Carriers develop glycosuria even before diabetes because of decreased renal glucose reabsorption [22]. Because hyperglycemia may be severe and worsens over time, the risks of microvascular and macrovascular complications are similar to type 1 diabetes mellitus (T1DM) and T2DM [23]. Therefore, tight glycemic control and close monitoring for diabetic complications are required in these patients.

Patients with HNF1A-MODY are sensitive to sulfonylurea therapy, which is recommended as first line treatment. An observational study suggests that patients with HNF1A-MODY can be switched safely from insulin to a sulfonylurea [24]. In a series of 43 diabetic patients, 34 switched from insulin to a sulfonylurea after HNF1A-MODY diagnosis, and 24 remained on sulfonylurea for 39 months with excellent glycemic control [25]. Good control may be maintained for many years, although most patients eventually progress to insulin treatment.

HNF4A-MODY (*MODY1*)

This was the first MODY to be described. HNF4A is a transcription factor that is expressed in the liver, intestine, kidney, and pancreatic islets. It is involved in the regulation of genes that are required for glucose transport and metabolism [26]. HNF4A mutations represent less than 10% of MODY cases in Europe, and more than 103 mutations in 173 families have been identified so far [19]. The clinical profile of heterozygous HNF4A mutations is similar to HNF1A MODY. It is estimated that 10% to 29% of HNF1A-negative patients actually have HNF4A mutations [27]. Patients with HNF4A diabetes are seldom diagnosed before adolescence. Heterozygous HNF4A mutations result in significant fetal macrosomia by increasing insulin secretion *in utero* and subsequent neonatal hypoglycemia [28]. Glycosuria does not present in HNF4A MODY, and low apolipoproteins (apoA11, apoCIII, and apoB) can be a diagnostic clue [29]. A similar response to sulfonylureas has been observed in patients with HNF4A-MODY [27].

PDX1-MODY (*MODY4*)

PDX1 (also known as insulin promoter factor 1 [IPF1]) is a homeodomain-containing transcription factor that acts in pancreas development and insulin gene expression [30]. Homozygous mutations can cause permanent neonatal diabetes due to pancreas agenesis [31]. Heterozygous PDX1 mutations lead to β-cell dysfunction and MODY. PDX1-MODY is a very rare cause of MODY and was first described in 1997 [32].

HNF1B-MODY (*MODY5*)

HNF1B is encoded by the TCF2 gene, which is expressed in the liver, kidney, intestine, stomach, lung, ovary, and pancreatic islets and influences their embryonic development [33]. This form of diabetes is caused by heterozygous mutations in HNFIB, and is characterized by progressive nondiabetic renal dysfunction of variable severity, pancreatic atrophy and genital abnormalities [34-36]. It is also called RCAD (renal cysts and diabetes syndrome). More than 65 mutations have been detected to date. Exon or complete gene deletions account for approximately half of cases [37]. A heterozygous P159L HNF1B mutation in a Korean family reportedly has functional consequences on glucose metabolism [38].

Birth weight can be significantly reduced by 900 g due to reduced insulin secretion *in utero* [35]. Half of carriers develop diabetes. Spontaneous de novo mutations occur relatively frequently; thus, a positive family history should not be required for diagnosis [39]. HNF1B-MODY phenotypes are different from HNF1A-MODY because diabetes develops due to both insulin resistance and defective insulin secretion. Patients with HNF1B-MODY do not respond well to sulfonylureas and usually require early insulin therapy [40].

***NEUROD1-MODY* (*MODY6*)**

NEUROD1 is a basic-loop-helix transcription factor that is involved in pancreatic and neuronal development. Heterozygous NEUROD1 mutations lead to diabetes as children or adults while mutations in both alleles result in neonatal diabetes with neurological abnormalities and learning disabilities [41-43].

***KLF11-MODY* (*MODY7*)**

KLF11 is a zinc-finger transcription factor that is expressed in pancreatic islet cells. KLF11 binds to and activates the insulin promoter in mouse insulinoma cell lines in a high-glucose condition, which indicates that KLF11 is a glucose-inducible regulator of the insulin gene [44]. Two rare variants of KLF11 gene were identified in three families with early onset T2DM [45].

***CEL-MODY* (*MODY8*)**

CEL is expressed in mammary glands and pancreatic acinar cells. CEL, also called bile salt-stimulated lipase, is a major component of pancreatic juice and is responsible for the hydrolysis of cholesterol esters as well as a variety of other dietary esters. CEL-MODY was first identified by Raeder et al. [46] in 2 Norwegian kindreds with autosomal dominant diabetes. Heterozygous mutations in the CEL gene result in pancreatic atrophy, fibrosis, and lipomatosis together with exocrine insufficiency and later endocrine dysfunction and diabetes [47].

***PAX4-MODY* (*MODY9*)**

PAX4 is a transcription factor that is essential for differentiation of insulin-producing β-cells in the mammalian pancreas. PAX4 gene mutations have been identified in Thai probands with MODY who did not have mutations in known MODY genes [48]. It has also been associated with ketosis-prone diabetes [49].

***INS-MODY* (*MODY10*)**

While INS gene mutations are a common cause of neonatal diabetes, they are also rare causes of diabetes in childhood or adulthood [50]. Heterozygous INS gene mutations decrease proinuslin molecule folding or cause β-cell apoptosis in the endoplasmic reticulum [51]. The treatment is generally insulin, although some patients manage with oral antidiabetic drugs.

***BLK-MODY* (*MODY11*)**

BLK is a non-receptor tyrosine-kinase of the src family of proto-oncogenes, which acts as a stimulator of insulin synthesis and secretion in pancreatic β-cells via the transcription factors Pdx1 and Nkx6.1 [52]. Kim et al. [53] initially mapped this locus on chromosome 8p23 by a genomewide scan of 21 extended United States families segregating autosomal dominant MODY not caused by known MODY genes. They noted that there was a higher prevalence of obesity in individuals with diabetes that was linked to 8p23 than in diabetic individuals with MODY linked to other loci. Borowiec et al. [52] reported that mutations in BLK caused diabetes in three families.

***ABCC8-MODY* (*MODY12*)**

The ABCC8 gene encodes the sulfonylurea receptor 1 (SUR1) subunit of the pancreatic β-cell ATP-sensitive potassium (K-ATP) channel. Its activating homo- and heterozygous mutations cause neonatal diabetes, but heterozygous mutations can also cause MODY in patients whose clinical features are similar to those with HNF1A/4A MODY [54]. The correct molecular diagnosis is important, as these patients can be treated with sulfonylureas.

***KCNJ11-MODY* (*MODY13*)**

The KCNJ11 gene encodes Kir6.2, a part of the K-ATP channel. Its activating homozygous mutations cause neonatal diabetes, but heterozygous mutations have been associated with a large spectrum of diabetes phenotypes in a French family [55]. The age at diagnosis varied from childhood to adulthood (13 to 59 years), and the treatment varied from diet to OAD or insulin. Of the 4 affected individuals, 2 maintained diabetes control with sulfonylurea therapy alone. Heterozygous KCNJ11 mutations were identified in Chinese family with early onset T2DM [56].

Table 2. MODY studies in Korean subjects

Gene	Subjects	Finding	Reference
HNF1A	69 early onset T2DM	One silent mutation	[58]
HNF1A	16 early onset T2DM	One missense (R236L) mutation	[20]
HNF1A	22 early onset T2DM	One mutation (promoter)	[59]
HNF4A, GCK, HNF1A	23 MODY and 17 early onset T2DM	One HNF1A (P393fsdelC, promoter) One GCK (R191W) One HNF4A (T130I polymorphism)	[5]
HNF1A	25 early-onset T2DM	Four promoter polymorphism	[60]
HNF1A	96 GDM	Five mutations (2 promoter, Arg278Gln, Pro300pro, IVS5 +106A>G)	[62]
HNF1B	1 MODY	One missense (P159L) mutation	[38]
PTPRD, SYT9, WFS1	6 MODY	Thr207Ile in PTPRD, Gln187Glu in SYT9, Val509Gly in WFS1 by whole-exome sequencing	[57]

MODY, maturity-onset diabetes of the young; HNF1A, hepatocyte nuclear factor 1 α; T2DM, type 2 diabetes mellitus; GCK, glucokinase; GDM, gestational diabetes mellitus; PTPRD, protein tyrosine phosphatase, receptor type, D; SYT9, synaptotagmin-9; WFS1, Wolfram syndrome 1.

MODY STUDIES IN KOREA

Although MODY has been identified in Asian populations, the prevalence of MODY is not known in Korea. In a study of Korean population, only 10% of 40 MODY or early onset T2DM patients had known MODY gene defects (HNF1A 5%, GCK 2.5%, and HNF1B 2.5%) among MODY 1-6 genes [5,6]. This result may be similar to reports from Japan and China [7,8]. The different genetic subtypes could possibly be responsible for Korean patients with MODY. Shim et al. [57] conducted whole-exome sequencing in Korean MODY families, and they could not find any Known MODY mutations but identified variants in protein tyrosine phosphatase, receptor type, D (PTPRD), synaptotagmin-9 (SYT9), and Wolfram syndrome 1 (WFS1). Mutation studies performed in Korean MODY or early onset T2DM patients are summarized in Table 2 [58-61].

MODY DIAGNOSIS

Although MODY represents 1% to 2% of all diabetes, MODY diagnosis is very important for patients and their families. A correct molecular diagnosis can help identify an optimal treatment strategy. Patients who have been on insulin therapy following T1DM diagnosis can be switched to oral agents (i.e., sulfonylureas) after a diagnosis of HNF1A-MODY or HNF4A-MODY, which will not only improve their quality of life but also often their glycemic control [24]. A molecular diagnosis of MODY can also affect patient prognosis. A patient with mild hyperglycemia in adolescence and a diagnosis of GCK-MODY, HNF1A-MODY, or T1DM will need different treatment and follow-up [13,23]. Finally, family members of affected MODY patients can be screened for their carrier status to predict disease. Genetic testing should be recommended to all family members, while unaffected relatives should receive genetic counseling regarding the benefits and potential consequences of genetic diagnosis.

MODY can be diagnosed by direct sequencing with up to 100% sensitivity [4]. Next generation sequencing strategies have been employed successfully to identify MODY gene mutations using gene targeted and whole-exome sequencing [62,63]. However, molecular genetic testing is expensive and is only available in specialized laboratories. Furthermore, the clinical features of MODY often overlap with both common types of diabetes. In a UK report, more than 80% of patients with MODY are incorrectly diagnosed with T1DM and T2DM at presentation, and patients experienced a delay of 12 years from the time of receiving a diabetes diagnosis to receiving a MODY diagnosis [64].

A targeted selection of individuals for molecular genetic testing is necessary to improve diagnostic yields especially in regions with limited resources. Various algorithms using clinical and laboratory parameters have been proposed to choose individual candidates for molecular diagnosis [65,66] Shields et al. [66] developed a model that discovered that age at diagnosis below 30 years was the most useful discriminator between MODY and T2DM, and a family history of diabetes increased the probability of MODY diagnosis by 23 times in those who had been initially labeled as T1DM. This model determines

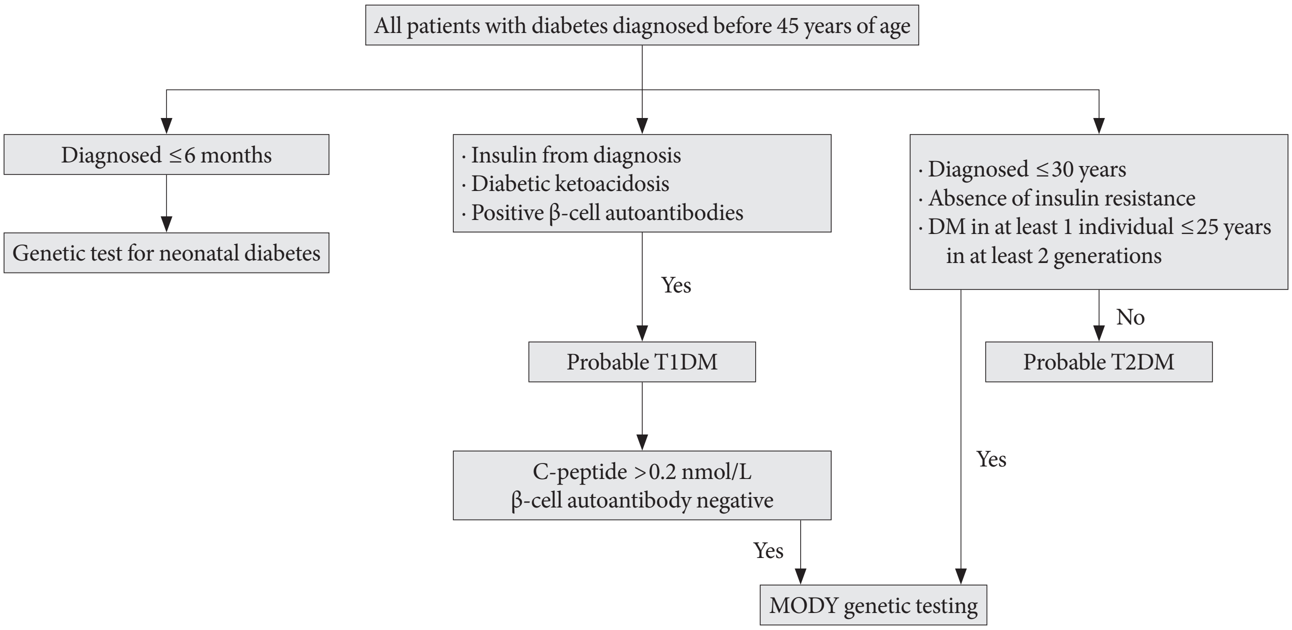

Fig. 1. Diagnostic algorithm for maturity-onset diabetes of the young (MODY). T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

the probability of MODY in young-onset diabetes (http://www.diabetesgenes.org/content/mody-probability-calcualtor).

The cost and limitations of accessing genetic testing has prompted much efforts to discover nongenetic biomarkers that might identify appropriate candidates for molecular diagnosis. Because patients with HNF1A-MODY have significantly lower levels of high-sensitivity C-reactive protein (hs-CRP) than those with other types of diabetes (T2DM, T1DM, and GCK-MODY), hs-CRP has been used as a marker for differential diagnosis [67-69]. A recent study raised the possibility of microRNAs as a biomarker of HNF1A-MODY [70]. Fig. 1 shows a diagnostic algorithm that could be used to identify which young adult with diabetes should be referred for MODY genetic testing.

CONCLUSIONS

MODY is a common cause of monogenic diabetes that constitutes 1% to 2% of all diabetes cases. Despite its low prevalence, identification of MODY genes has implications in diabetes pathogenesis. Various clinical characteristics of MODY can be explained by genetic heterogeneity. The advance of molecular genetics and clinical science has led to specific treatment for MODY subtypes. This is an excellent example of personalized medicine in the field of diabetes. Rapid MODY diagnosis is important for patients and their family members because it can provide for individualized treatment and prognosis predictions. However, diagnosing MODY is a challenge for physicians and the vast majority of cases remain unidentified. A nationwide MODY registry and systematic approaches are required for the rapid diagnosis and appropriate management of MODY.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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