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Maturity-onset Diabetes of the Young: Update on Diagnosis and Treatment

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Maturity-onset diabetes of the young (MODY) is characterized by a heterogeneous group of monogenic diabetes. MODY has autosomal dominant inheritance, a primary defect in pancreatic β-cell, and an early onset. Discriminating MODY from type 1 or type 2 diabetes is often challenging at first. To date, 14 different disease causing mutations have been identified in MODY patients worldwide. Targeted DNA sequencing is the gold standard to diagnose MODY and their asymptomatic relatives. Next-generation sequencing may help successfully to diagnose MODY patients and identify new MODY genes. In this review, the current perspectives on diagnosis and treatment of MODY and discrepancy in the disease-causing mutations between the Asian and Caucasian patients with MODY are summarized.

Key words: Diabetes mellitus, Genes, Sequencing, MODY

REVIEW ARTICLE

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INTRODUCTION

Mutations in the genes that control insulin secretion cause maturity-onset diabetes of the young (MODY) [1,2]. MODY was first reported in 1974 as a mild familial diabetes with dominant inheritance [1]. MODY is characterized by β-cell dysfunction without autoantibodies, autosomal dominant inheritance and onset before 45 years of age [3]. MODY is not easily distinguished from type 1 diabetes and type 2 diabetes at diagnosis. Type 1 diabetes differs from MODY, in terms of pathogenesis of pancreatic β-cell auto-immunity. MODY patients have maintained β-cell function. Type 2 diabetes resembles MODY patients, but, type 2 diabetes patients are generally obese, and have insulin resistance.

To date, at least 14 MODY subtypes are reported (Table 1) [4-11]. MODY is rare disease, comprising between 1-5% of all diabetes cases in Europe [12,13]. Mutations in glucokinase (GCK), hepatocyte nuclear factor 1α (HNF1A), HNF4A, and HNF1B are the most commonly identified causes in more than 95% cases of MODY, respectively, 32%,52%,10%, and 6% of diabetes patients in the United Kingdom [14]. However, there is a big discrepancy among Asian and Caucasian populations. Clinical MODY patients have been known with MODY-related gene defects (GCK, 22.8%; HNF1A, 13.9%; HNF4A, 3.8%, and HNF1B, 7.6%) in Japan, whereas the causative mutations were not identified in 51.9% [15]. This suggests that there are unidentified MODY related genes in Asia. Moreover, the exact prevalence of MODY in the Asian population has not been reported. This review summarizes the current perspective on understanding of MODY and discusses the Asian MODY study.

Table 1. Causative genes and their clinical characteristics of MODY subtype

Subtype	MODY gene	Chromosome location	Gene function	Pathophysiology	Other features	Treatment
MODY 1	HNF4α	20q13	Transcription factor	β-cell dysfunction	Hyperinsulinism during infancy, Low triglycerides level	Sulfonylureas
MODY 2	GCK	7q13	Enzyme in the first step of glucose metabolism	β-cell dysfunction	Mild fasting hyperglycemia	No medications, Diet
MODY 3	HNF1α	12q24	Transcription factor	β-cell dysfunction	Glycosuria	Sulfonylureas
MODY 4	PDX1	13q12	Transcription factor	β-cell dysfunction	Pancreatic agenesis in homozygote/compound heterozygote	Diet or OAD or insulin
MODY 5	HNF1β	17q12	Transcription factor	β-cell dysfunction	Renal anomalies, genital anomalies, pancreatic hypoplasia	Insulin
MODY 6	NEUROD1	2q31	Transcription factor	β-cell dysfunction	Neonatal diabetes, Neurological abnormalities in homozygote	OAD or insulin
MODY 7	KLF11	2q25	Transcription factor	β-cell dysfunction	Similar with type 2 diabetes	OAD or insulin
MODY 8	CEL	9q34	Controls exocrine and endocrine functions of pancreas	Pancreas endocrine and exocrine dysfunction	Exocrine dysfunction, lipomatosis	OAD or insulin
MODY 9	PAX4	7q32	Transcription factor	β-cell dysfunction	Possible ketoacidosis	Diet or OAD, or insulin
MODY 10	INS	11p15	Encode the proinsulin precursor	Insulin gene mutation	PNDM	Diet or OAD, or insulin
MODY 11	BLK	8p23	Tyrosine kinase functions in signal transduction	Insulin secretion defect	Overweight	Diet or OAD, or insulin
MODY 12	ABCC8	11p15	Regulating insulin release	ATP-sensitive potassium channel dysfunction	PNDM , TNDM	Sulfonylurea
MODY 13	KCNJ11	11p15	Regulating insulin release	ATP-sensitive potassium channel dysfunction	Neonatal diabetes in homozygote	OAD or insulin
MODY 14	APPL1	3p14	Insulin signal pathway	Insulin secretion defect	Dysmorphic phenotype, developmental delay	Diet or OAD, or insulin

MODY, maturity-onset diabetes of young; HNF4α, hepatocyte nuclear factor 4α; GCK, glucokinase; PDX1, pancreatic and duodenal homeobox 1; HNF1β, hepatocyte nuclear factor1β; NEUROD1 neurogenic differentiation 1; KLF11, kruppel-like factor 11; CEL, carboxyl ester lipase; PAX4, paired-box-containing gene 4; INS, insulin; BLK, B-lymphocyte kinase; ABCC8, ATP-binding cassette, subfamily C(CFTR/MRP), member 8; KCNJ11, potassium channel inwardly rectifying subfamily J, member 11, APPL1, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; OAD, oral antidiabetic agent; PNDM, permanent neonatal diabetes; TNDM, transient neonatal diabetes.

MODY SUBTYPES AND THEIR CLINICAL FEATURES

HNF1A-MODY (MODY 3)

Hepatocyte nuclear factor 1α is a homeodomain-containing transcription factor expressed in liver, kidney, pancreatic β-cell, and intestine. More than 400 HNF1A mutations have been reported in 1,247 families [16]. A mutation in exon 4 of the gene (P291fsinsC) is most frequently reported [16,17]. A missense mutation of HNF1A (R263L) has been reported in a Korean MODY, causing defective insulin secretion [18]. Mutations in HNF1A have high penetrance, and approximate 63% carriers develop diabetes by the age of 25, and almost all carriers develop diabetes by the age 55 [19]. Because HNF1A is expressed in various organs, patients with HNF1A MODY develop glycosuria even diabetes, due to a low renal threshold of glucose sensing [20]. Heterozygous mutation in HNF1A gene cause β-cell dysfunction, and patients with this mutation have the similar risk of long-term complications over the time to those in type 1 and type 2 diabetes [21]. Therefore, tight glucose control and close monitoring for these patients are need. Patients with HNF-1MODY have high sensitivity to the sulfonylurea treatment, which is a five-greater response than metformin and is considered for first line treatment [22]. Many studies have been reported that many patients with HNF-1 MODY might switch from insulin to a sulfonylurea [23].

GCK-MODY (MODY 2)

GCK is an enzyme which catalyzes the conversion of glucose to glucose-6-phosphate in glucose metabolism, and controls glucose-related insulin secretion. Heterozygous mutations in GCK develop GCK-MODY, known as MODY-2. More than 600 mutations in GCK have been identified [24]. The heterozygous mutation in GCK cause elevated glucose thresh-

old for insulin release, developing mild fasting hyperglycemia [25]. According to Japan study, MODY 2 is most common form in MODY subtype, comprising approximately 48% of patients with MODY [15]. This result is similar to that in European MODY patients [26]. Therefore, most of MODY 2 is diagnosed through routine examination, as urine glucose screening test. Hence, MODY 2 has high prevalence in countries where routine urinary screening test is performed [27,28]. However, only a small number (< 5%) about MODY 2 was reported in Korea and China [29,30]. Therefore, this suggests that there is a big discrepancy between the Asian and Caucasian populations. The clinical manifestations comprise mild fasting hyperglycemia (5.5-8.0 mmol/L, glycosylated hemoglobin range of 5.6-7.3%) [25] which from birth, demonstrates slightly aggravations with getting old. Therefore, MODY 2 patients usually do not need treatment, outside pregnancy, because their diseases are non-progressive, and they rarely develop long-term complications [31].

HNF4A-MODY (MODY1)

HNF4A is also a transcription factor which is expressed in diverse organ such as the intestine, liver, pancreatic β-cell, and kidney. This regulates genes related to glucose transport and metabolism [32]. HNF4A-MODY is rare, comprising only approximately 5% cases of all MODY, more than 103 mutations have been identified [16,33]. The clinical manifestation of HNF4A is similar to that in HNF1A. Heterozygous HNF4A are usually not diagnosed before adolescence. Unlike HNF1A-MODY patients, MODY1 patients don't present glycosuria, low level of apolipoproteins might be a clue for diagnosis [34]. HNF4A-MODY has similar response to sulfonylurea, therefore, sulfonylurea should be considered as the first-line treatment [22].

PDX1-MODY (MODY 4)

PDX1 is known as insulin promoter factor 1 (IPF1) which is a homeodomain-containing transcription factor, regulating development of β-cell and insulin release in pancreas [35]. MODY 4 is very rare, and was first reported in 1997. Heterozygous IPF1 gene mutation causes β-cell dysfunction and homozygous mutation develop permanent neonatal diabetes due to pancreas agenesis [36].

HNF1β-MODY (MODY 5)

The transcription factor HNF1β is associated with the organogenesis of the pancreas, liver, kidney, lung, gut and genitourinary tract [37]. Patients with mutation in HNF1β have kidney disease such as renal cysts, renal tract malformations, and familial hypoplastic glomerulocystic kidney disease [38, 39]. It is called RCAD (renal cysts and diabetes) syndrome. Renal dysfunction is usually developed in affected patients by 45 years of age, and approximately half of these patients will progress to end-stage renal disease without diabetic renal disease [40]. Until now, more than 65 mutations have been identified. Approximate half of mutations comprise exon or complete gene deletions [41]. A heterozygous P159L mutation in *HNF1B* was reported in a Korean family and this pathogenesis was discovered [42,43]. Half of carriers develop diabetes in early adulthood. In contrast to patient with MODY 3, MODY 5 patients progress to an insulin-dependent condition due to pancreatic hypoplasia. Patients harboring same HNF1β mutations show highly variable manifestations, which might exhibit different phenotype between family members.

NEUROD1-MODY (MODY 6)

NEUROD1 is a basic-loop-helix transcription factor, which is associated with pancreatic and neuronal development. Heterozygous mutations lead to diabetes in childhood or early adult. Whereas, homozygous mutations develop neonatal diabetes, neurological abnormalities [44,45].

WAY TO CORRECTLY DIAGNOSE PATIENTS WITH MODY

MODY shows similar clinical manifestations with both common types of diabetes. Therefore, discriminating MODY from type 1 diabetes or type 2 diabetes is often challenging at first visit [12,46,47]. The diagnostic criteria comprise 1) presence of overt diabetes at least three consecutive generations with autosomal dominant pattern, 2) diagnosis with diabetes before the age of 25, 3) absence of β-cell autoantibodies, 4) relatively preserved endogenous insulin secretion with a serum C-peptide level of > 200 pmol/L [12,46,47].

MODY can be detected by direct sanger DNA sequencing with up to 100% sensitivity [14,43]. Using targeted or whole-exome gene sequencing for MODY is gold standard to identify disease-causing mutations in MODY (Fig. 1). However, genetic testing for patients with MODY is not cheap, and may only be available in specialized laboratories. Molecular genetic testing is needed in targeted selection of individuals. Various algorithms have been developed to choose individual candidates who should get genetic testing for MODY [48,49]. Shield et al.

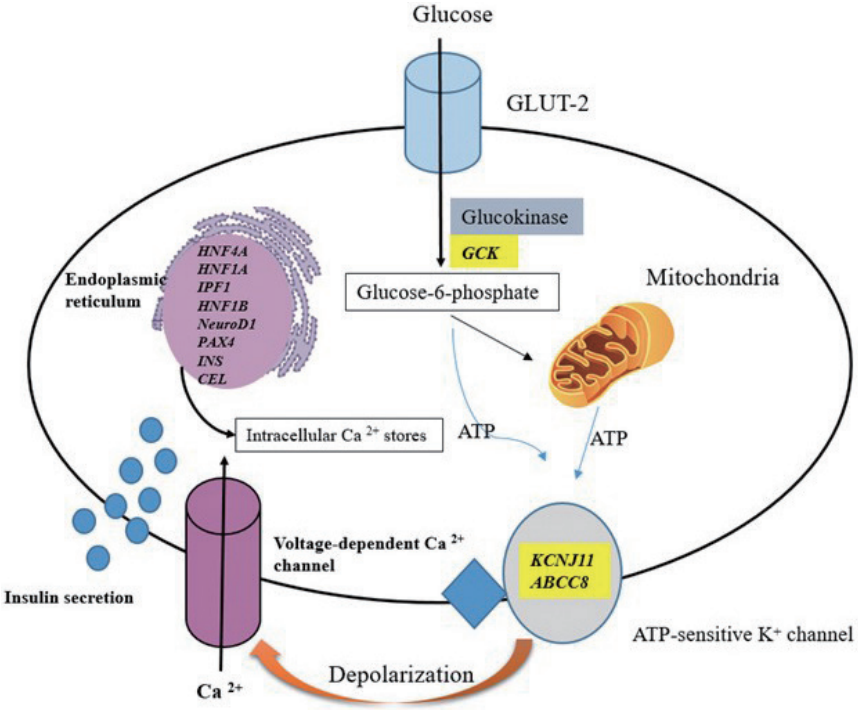

Fig. 1. Schematic representation of MODY-causing genes in pancreatic β cells and mechanism of glucose induced insulin secretion. HNF4A, hepatocyte nuclear factor 4α; HNF1A, hepatocyte nuclear factor 1α; IPF1, insulin promoter factor-1; HNF1B, hepatocyte nuclear factor1β; NeuroD1, neurogenic differentiation 1; PAX4, paired box-containing gene 4; INS, insulin gene; CEL, carboxyl ester lipase; GCK, glucokinase; KCNJ11, potassium channel inwardly rectifying subfamily J, member 11; ABCC8, ATP-binding cassette, subfamily C (CFTR/MRP), member 8.

[48] have developed a clinical model to discriminate MODY from type 1 and type 2 diabetes. According to this report, MODY has lower $HbA1_C$ than type 1 diabetes and 23 times more family history of diabetes than type 1 diabetes. MODY has lower $HbA1_C$ level, a lower body mass index (BMI), and younger age at diagnosis.

The genetic causes of MODY have been widely reported. Although MODY has been identified in Caucasian populations, the exact prevalence of MODY is not reported in Korea. According to recent Korea study, clinically suspected MODY patients underwent targeted MODY sequencing [50]. The diagnostic yield was similar to those in large study conducted in the United Kingdom (27%) [51]. In Korea study, 40 subjects as suspected MODY showed only 5% MODY3 and 2.5% MODY 2 [52]. This result is similar to those in China and Japan [30,53]. This reports suggest that East Asia might have high possibilities of a not yet identified 'MODY X' [30,50,53-56]. Therefore, there are attempts to identify new MODY gene by whole-exome sequencing [9]. Next generation sequencing is good tools to find unidentified genetic defects [56,57]. Furthermore, there are many attempts to discover new causative gene variants in MODY patients by whole exome sequencing in Korea [9].

CONCLUSION

MODY is a common cause of monogenic diabetes, comprising 1-2% of all diabetes causes. Despite of low incidence, identification of MODY gene has importance because correct diagnosis can help MODY patients receive individualized treatment.

Direct sequencing is best way to diagnose MODY patients, however, there are unidentified MODY gene. Therefore, efforts to identify new MODY gene and systemic approaches for MODY patients are needed for rapid diagnosis and proper treatment.

CONFLICTS OF INTEREST

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

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