Maturity-onset diabetes of the young (MODY): Recognition is the need of the hour

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ABSTRACT

Maturity-onset diabetes of the young (MODY), which is inherited as an autosomal dominant disease, is a monogenic form of diabetes with early-onset diabetes, and mostly mild hyperglycemia resulting from pancreatic β -cell dysfunction. MODY gets commonly misdiagnosed as type 1 or type 2 diabetes mellitus, which represents less than 2% of all diabetes cases. It is a genetically heterogeneous form of monogenic diabetes that is caused by mutations occurring in different genes thus tends to cause a slightly different variant of diabetes. At least 14 MODY subtypes with distinct genetic etiologies have been identified. Typically, MODY is diagnosed during late childhood, adolescence, or early adulthood but can occasionally develop in adults during their late 50's. One of the main drawbacks of diagnosing MODY is that many people are misdiagnosed as having type 1 or type 2 diabetes due to a low index of suspicion and non-availability of genetic testing at an affordable cost. Nonetheless, a molecular and genetic diagnosis results in better treatment and could also help in identifying other family members with MODY. Misdiagnosing MODY as type 1 diabetes may have a significant impact on the quality of life (QOL) with increased cost and unnecessary treatment with insulin, and therefore a high index of suspicion is required to diagnose cases.

Keywords: Maturity Onset Diabetes of Young (MODY), gene mutation, monogenic diabetes.

JMS: 2019; 22(2):3-11 DOI: <https://doi.org/10.33883/jms.v22i2.486>

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder with widespread implications on the social, economic, and health status of an individual. It is fast emerging as a global epidemic affecting almost all the countries irrespective of the socioeconomic conditions. Apart from micro and macro-vascular complications, diabetes mellitus patients are at risk of specific fatal infections¹. According to the International Diabetes Federation estimates, around 425 million people had DM in 2017, and this number is expected to rise to 629 million by 2045². As per the estimate, 75 % of patients with diabetes live in middle and low-income countries³. Type2 diabetes (T2DM) is the most common type of this disorder followed by type 1 diabetes (T1DM), both of which account for more than 95% of cases. Less frequent causes include pancreatic diabetes, monogenic diabetes, and other secondary forms of DM. Maturity onset diabetes of the youth (MODY) is characterised by

autosomal dominant inheritance affecting three or more successive generation, early onset of diabetes, lack of features of insulin resistance or signs related to the autoimmune process, preservation of endogenous insulin secretion^{4,5} and mild hyperglycemia in some forms and better prognosis. The symptoms of this disease manifest slowly with the absence of obesity and ketosis in most cases. MODY is the result of heterozygous mutations in various transcription factors. These mutations involve genes coding for transcription factors involved in beta cell development, differentiation, and survival⁶ in addition to enzymes involved in glucose sensing of the pancreatic β -cell resulting in a unique form of early-onset diabetes⁷.

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Access this article online

Website:
www.jmsskims.org

DOI:
<https://doi.org/10.33883/jms.v22i2.486>

How to cite this article: Bhat JA, Bhat MH, Masoodi SR. Maturity-onset diabetes of the young (MODY): Recognition is the need of the hour. jms 2019;22(2):3-11

Received: 30-11-2019 Accepted: 04-12-2019

Historical aspects

Maturity Onset Diabetes of the Young was first described by Fajans and Conn⁸, who first reported youth onset diabetic patients who were not dependent on insulin. Later Tattersall (1974) from King's College, London, published a report entitled "Mild familial diabetes with dominant inheritance," where he described three families with an autosomal dominant form of diabetes. This form of diabetes had early onset, mild hyperglycemia, and relatively uncomplicated course. In these families, they found that seven out of 12 diabetes patients diagnosed under the age of 30 had no retinopathy after an average duration of 37 years. In these two families studied, diabetes was associated with a low renal threshold for glucose. They noted an autosomal dominant pattern of the disease in these families in addition to evidence of the genetic heterogeneity of diabetes mellitus⁹.

Further evidence for a separate autosomal dominant form was provided by Tattersall and Fajans (1975) and by Johansen and Gregersen (1977)^{10,11}. The term MODY was first used by Tattersall and Fajans, who used first letters of the new entity in diabetes called Maturity onset diabetes of young, in their paper titled "A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people." They also laid down the criteria for the diagnosis of MODY¹². Nelson and Pyke (1976) referred to this as maturity-onset diabetes of the young while describing three families with this different kind of diabetes¹³. It has also been called the Mason type, after the family in which it was first observed¹⁴.

Prevalence

MODY is the commonest form of monogenic form of diabetes. MODY represents 1-2% of patients diagnosed with diabetes and accounts for less than 1% - 2.4% of the pediatric diabetes population (1517). Recent studies have reported a MODY prevalence of 21-45/1,000,000 children and 100/1,000,000 adults (1920), but prevalence estimates will not be accurate until large population screening studies are performed²¹.

The prevalence of MODY in different populations is still unknown. A study by Panzram, done almost five decades back, is the only study that examined the prevalence of MODY in the general population and found it to be 0.15%²². In southern India prevalence of MODY was estimated to be

4.8% among patients of non-insulin dependent diabetes mellitus (NIDDM) who had age at diagnosis below 25 years, 18.5% below 35 years and almost 50% below 45 years²³, suggesting a higher prevalence of MODY among Indian patients.

It has been reported that MODY is not a common form of diabetes among the white population²². However, a number of reports from Europe and the United States have confirmed the existence of MODY^{22,24-27}. The prevalence of MODY is higher than previously thought in certain communities of the world. The higher rates of prevalence ranging from 4.8%-10% have been shown in studies involving Pima Indians, Nauru population, and also in Asian Indians in South Africa and southern India^{22-23, 27-28}. A study was conducted in Kashmir valley to determine the prevalence of MODY among diabetic patients aged <25 years of age and found a prevalence of 7.7%, with an increase in prevalence with increasing age in the disease onset in the patient cohort. Forty patients of clinically identified MODY were subjected to the amino acid polymorphism (SNP) of Ala>Val on codon 98 in the HNF1 α gene (MODY 3), the mutant genotype was seen in 50% of patients (unpublished).

Genetic classification and clinical types of MODY subtypes

There is wide clinical, metabolic, and genetic heterogeneity within and among the different subtypes of MODY. So far, 14 types of mutations responsible for the same number of MODY types have been elucidated (Table 1). Novel MODY-causing genes are still being defined, and their roles in the pathogenesis of diabetes are being investigated²⁹. It is believed that many MODY-related genes have not yet been identified (30).

The first MODY gene to be documented was glucokinase (GCK)³¹⁻³², followed by hepatocyte nuclear factors- HNF1 α (TCF1) and HNF4 α ^{33, 34}. They encode glucokinase and transcription factors that are responsible for the early processing of glucose in the β -cell, thus acting as a glucose sensor for beta cells and transcription factors that modulate the expression of numerous genes concerned with the growth, proliferation, and differentiation of β -cells respectively. In a study by Shields et al, over 99% of MODY with a known genetic etiology results from mutations in HNF1 α , HNF4 α , or GCK¹⁸. Although mutations in other genes have been shown to cause MODY⁸, they are very rare.

Specific subtypes and their properties

GCK-MODY (MODY2)

The conversion of glucose to glucose-6-phosphate inside the pancreatic β -cell is catalysed by a glycolytic enzyme-glucokinase (GCK), which is also referred to as the β -cell glucose sensor because it controls glucose-mediated insulin release. Heterozygous inactivating mutations of this enzyme (GCK) cause GCK-MODY, which is also known as MODY2. This entity was first recognized in 1992³¹.

HNF1 α -MODY (MODY3)

Heterozygous mutation in the transcription factor HNF1 α result in progressive β -cell dysfunction and leads to diabetes in early adult life. A high penetrance is demonstrated by these mutations; by 25 years of age, almost 63% of carriers develop diabetes, and almost all carriers develop diabetes by the age of 55³⁵. The mean age of MODY3 diagnosis in children is 14 years (range 4-18 years) and is rarely identified in children younger than ten years³⁶.

HNF4 α -MODY (MODY1)

The transcription factor HNF4 α is expressed mainly in the liver in addition to pancreatic islets and kidneys, and affects glucose metabolism, which results in hyperglycemia. The clinical profile of heterozygous HNF4 α mutations is similar to HNF1 α MODY. Patients with MODY1 diabetes are never diagnosed before adolescence.

PDX1-MODY (MODY4)

PDX1 homeodomain-containing transcription factor, described first in 1997, is a very rare cause of MODY³⁷. Permanent neonatal diabetes is caused by homozygous mutations³⁸, while heterozygous mutations lead to β -cell dysfunction and MODY³⁷.

HNF1 β -MODY (MODY5)

HNF1 β is expressed in the early phase of embryonic development in the pancreas, kidneys, liver, and genital tract. Developmental abnormalities may, therefore, be encountered in all of these organs in individuals with **HNF1 β** mutations. MODY5 is characterized by progressive non-diabetic renal dysfunction of variable severity, pancreatic atrophy, genital abnormalities, gallbladder dysfunction, gout, and hyperuricemia³⁹⁻⁴¹. RCAD (renal cysts and diabetes syndrome) is another name

for MODY5.

NEUROD1-MODY (MODY6)

NEUROD1 gene regulates the development of the pancreas and **INS** expression. The majority of the patients with this mutation are obese. Heterozygous **NEUROD1** mutations lead to diabetes in children and adults, while homozygous mutations result in neonatal diabetes with neurological abnormalities, vision, hearing, and learning disabilities⁴²⁻⁴⁴.

CEL-MODY (MODY8)

CEL, also called bile salt-stimulated lipase, is expressed in mammary glands and pancreatic acinar cells, 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. In a study by Johansson et al, it was observed that patients with heterozygous mutations of **CEL** had exocrine pancreatic dysfunction during childhood and diabetes mellitus in adulthood. Also, it was found that these patients had pancreatic atrophy, fibrosis, and lipomatosis on histopathology⁴⁵.

ABCC8-MODY (MODY12)

The **ABCC8** gene is located on chromosome 12. It encodes the sulfonylurea receptor 1 (**SUR1**) subunit of ATP-sensitive potassium channel on pancreatic β cells. Activating mutation of **ABCC8** (homozygous or heterozygous) causes neonatal diabetes; however, heterozygous mutations of this gene also cause MODY, which is similar to HNF1A/4A MODY⁴⁶. It is important to diagnose these patients correctly, as these patients are very sensitive to sulfonylureas.

KCNJ11-MODY (MODY13)

The **KCNJ11** gene encodes Kir6.2, a part of the ATP-sensitive potassium channel. Its activating homozygous mutations cause neonatal diabetes, but heterozygous mutations have been associated with MODY13. MODY13 is diagnosed from childhood to adulthood (13 to 59 years), and the treatment varied from diet to OAD or insulin⁴⁷.

Other than the types of MODY described above, there are a number of very rarer forms that have been described, but their contribution to the burden of diabetes is almost negligible. These rarer forms include MODY7 (**KLF11**), MODY9 (**PAX4**), MODY10 (**INS**), MODY11 (**BLK**), and MODY14 (**WFS**).

Table 1. Genetic classification and clinical phenotypes and treatment of the MODY subtypes.

MODY	Gene	Locus	Clinical features	Treatment
MODY1	Hepatocyte nuclear factor 4 α (HNF4A)	20q12–q13.1	Mild-severe fasting and postprandial plasma glucose (PG). Progressive insulin secretory defect. Fetal macrosomia, transient neonatal hypoglycemia	Respond well to sulphonylurea agents
MODY2	Glucokinase(GCK)	7p15–p13	Mild fasting hyperglycemia. Asymptomatic/abnormal OGTT/ GDM /LBW. Less than 50 % of carriers have overt diabetes and microvascular complications of diabetes are rare	Treatment not needed except in pregnancy.
MODY3	Hepatocyte nuclear factor 1 α (HNF1-A)	12q24.2	The most common type of MODY. Familial, early-onset diabetes and renal glycosuria	Typically insulin is not immediately required. Often responds well to sulphonylurea pills
MODY4	Insulin promoter factor-1 (IPF-1/PDX)	13q12.1	Very rare, mild diabetes (in the heterozygous form), Pancreatic agenesis in homozygous form	Diet or OAD or insulin
MODY5	Hepatocyte nuclear factor 1 β (HNF1-B)	17cen–q21.3	Overt diabetes in association with renal (RCAD), genitourinary abnormalities, pancreatic atrophy, exocrine dysfunction, hyperuricemia	Insulin
MODY6	Neurogenic differentiation 1 (NEUROD1)	2q32	Rare; the phenotype is characterized by obesity and insulin resistance.	OAD or insulin
MODY7	Kruppel-like factor 11 (KLF11)	2P25	Very rare, phenotype varies in glucose tolerance, from impaired glucose tolerance or impaired fasting glucose to overt diabetes. Pancreatic atrophy, exocrine pancreatic dysfunction	OAD or insulin
MODY8	Bile salt-dependent lipase (CELL)	9q34.3	Very rare; characterised by both exocrine and endocrine pancreatic deficiency with demyelinating peripheral neuropathy and lipomatosis	OAD or insulin
MODY9	Paired Domain gene 4 (PAX4)	7q32	Very rare. Crucial transcription factor for beta cells development	Diet or OAD or insulin
MODY10	Insulin (INS)	11p15.5	Very rare. Usually associated with neonatal diabetes. < 1 % cases.	OAD or insulin
MODY11	Tyrosine kinase, B-Lymphocyte specific (BLK)	8p23–p22	These adapter proteins' nucleate formation contributes to the qualitative and quantitative control of beta-cell signaling.	Diet or OAD or insulin
MODY12	ABCC8	11p15.1	Very rare. Usually associated with neonatal diabetes. < 1 % cases.	OAD (sulfonylurea)
MODY13	KCNJ11	11p15.1	Very rare. Usually associated with neonatal diabetes. < 1 % cases.	Diet or OAD or insulin
MODY14	WFS	4p16.1	Rare. Usually associated with DIDMOAD syndrome. Also, seen with early-onset diabetes. < 1 % cases.	Diet or OAD or insulin

MODY: Maturity-onset diabetes of the young, GCK: Glucokinase, CEL: Carboxy ester lipase, RCAD: Renal cyst and diabetes, OAD: Oral antidiabetic drug.

Diagnosis

The accurate diagnosis of MODY has not only the clinical implication in the treatment modalities and cost of the management of disease but also the socioeconomic outlook of the disease besides having a definite out bearing on the clinical outcome and course of the disease. The clinical implications of an accurate MODY diagnosis include: i) treatment modality, ii) determination of the natural progression of MODY, iii) familial screening, iv) management of MODY during pregnancy, and v) MODY as a model for the study of the β -cell.

Typically MODY is diagnosed during late childhood, adolescence, or early adulthood but has been known to develop in adults as old as 50 years. 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 or type 2 diabetes mellitus¹⁸ thus the most under-diagnosed condition. MODY must be distinguished from type 1 and type 2 diabetes as optimal treatment and inheritance is different. Furthermore, the probability of inheriting the same mutation is 50% among the first degree relatives, which confers a greater than 95% lifetime risk of developing diabetes⁴⁸.

The clinical diagnosis of MODY laid down by Tattersall and Fajans¹⁰ is usually based on the following criteria: i) age at diagnosis below 25 years, ii) control of fasting hyperglycemia without insulin for a minimum of 2 years, and iii) absence of ketosis at any time. Later, Tattersall suggested to extend the period, without insulin, to 5 years, to completely exclude insulin-dependent diabetes mellitus (IDDM) patients, who might initially respond to oral agents. It has also been suggested that autosomal dominant inheritance should be used as a diagnostic criterion.

MODY is particularly suspected in individuals meeting these criteria who are lean and not from ethnic groups with a high prevalence of type 2 diabetes (e.g., African American, Hispanic, and Pacific Islander). Lack of these type 2 diabetes risk factors and type 1-diabetes specific markers including diabetes auto-antibodies and low C-peptide (as a measure of endogenous insulin production) can be evaluated to differentiate the *probability* of MODY from early-stage type 1 diabetes and type 2 diabetes, but these risk factors including adiposity do not completely differentiate the diagnoses. So clinical definition for

diagnosis is no longer sufficient to make the diagnosis, but it should be supplemented with genetic testing to confirm, diagnose, and classify MODY. According to the International Society for Pediatric & Adolescent Diabetes (ISPAD), a diagnosis of monogenic diabetes cannot be made now without genetic testing⁴⁹.

The field of genetics is rapidly advancing due to decreasing costs and increasing the capabilities of next-generation sequencing (NGS). By direct sequencing, MODY can now be diagnosed with up to 100% sensitivity (50). MODY gene mutations can be successfully identified by next-generation sequencing strategies using gene-targeted and whole-exome sequencing^{29, 51}. However, molecular genetic testing is still expensive and is only available in specialized laboratories.

In limited-resource countries, a targeted selection of patients for molecular genetic testing is necessary to improve diagnostic yields. Various clinical and laboratory parameters have been proposed in different algorithms to choose correct candidates for molecular diagnosis^{52, 53}. A model developed by Shields et al.⁵³ found that age at diagnosis below 30 years was the most useful discriminator between MODY and T2DM. They also found that 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 the probability of MODY in young-onset diabetes (<http://www.diabetesgenes.org/content/mody-probability-calculator>).

In recent years, researchers have attempted to identify inexpensive and widely available biomarkers that are sensitive and specific for identifying persons with MODY. C-reactive protein (CRP) has exhibited the most promise for identifying HNF1 α -MODY but no other MODY subtypes^{54, 55}. Since HNF1- α is a regulator of fucosylation of proteins, the examination of plasma glycoprotein profiles can indicate *HNF1A* damaging variants⁵⁶. A major downside of this metabolite marker is that there is no high-throughput technique for this measure. Other metabolites, including CD36, cystatin C, and ghrelin, have also been studied for the same purpose, but to less extent than CRP or glycoprotein profiles⁵⁷.

Treatment

The treatment of individuals with MODY2 (GCK MODY) is not recommended because hyperglycemia is mild, and

microvascular complications are not encountered^{7,58}. In addition, no change is observed in HbA1c values after discontinuing treatment with insulin or oral hypoglycemic agents^{42, 59}. The exception is pregnant women, in whom insulin may be required to prevent fetal overgrowth and subsequent maternal and fetal complications associated with macrosomia.

Sulfonylureas have been found to be the treatment of choice in the case of individuals with MODY3 and MODY1. A low-dose sulfonylurea (e.g., 20-40 mg/day gliclazide) is the preferred long-term treatment. It has also been reported that gliclazide improved fasting blood glucose levels by 5.2-fold compared with⁶⁰. Similar sulphonylurea efficacy has been described in MODY3/MODY1 patients⁶¹, with the exception of a small (about 15%) subgroup of HNF4- α MODY patients with the p.R114W mutation who have different phenotype including reduced sensitivity to low doses of sulphonylureas⁶². The optimal treatment for MODY3/MODY1 outside pregnancy is Sulphonylureas and glibenclamide.

In general, patients with MODY3 develop sulfonylurea unresponsiveness after 3-25 years due to the progressive decrease in insulin secretion (1-4% decrease each year) and become insulin-dependent in adulthood⁶³. A similar response to sulfonylureas has been reported in patients with MODY1⁶⁴. Patients with MODY5 do not generally respond to sulfonylureas and typically require insulin early on in their disease. Moreover, these patients have been reported to develop microvascular complications⁶⁵.

Conclusion MODY is a rarer form of diabetes; however, its presence has been reported from across the world. Being a highly penetrant genetic form of diabetes, its presence needs to be recognized accurately in order to provide appropriate treatment. A high index of suspicion is required to diagnose cases of MODY as misdiagnosis, and inappropriate treatment may have a significant impact on the quality of life (QOL) with increased cost and unnecessary treatment with insulin. Since etiology-specific treatment of MODY can have a drastic improvement in patient care, the implementation of genetic testing needs to be emphasized and made available everywhere. While improving MODY diagnosis will certainly improve the clinical care for patients, it will also have broader implications.

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