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MINI REVIEW

Precision diabetes: Lessons learned from maturity-onset diabetes of the young (MODY)

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ABSTRACT

Maturity-onset of diabetes of the young (MODY) are monogenic forms of diabetes characterized by early onset diabetes with autosomal dominant inheritance. Since its first description about six decades ago, there have been significant advancements in our understanding of MODY from clinical presentations to molecular diagnostics and therapeutic responses. The prevalence of MODY is estimated as at least 1.1–6.5% of the pediatric diabetes population with a high degree of geographic variability that might arise from several factors in the criteria used to ascertain cases. *GCK*-MODY, *HNF1A*-MODY, and *HNF4A*-MODY account for >90% of MODY cases. While some MODY forms do not require treatment (i.e., *GCK*-MODY), some others are highly responsive to oral agents (i.e., *HNF1A*-MODY). The risk of micro- and macro-vascular complications of diabetes also differ significantly between MODY forms. Despite its high clinical impact, 50–90% of MODY cases are estimated to be misdiagnosed as type 1 or type 2 diabetes. Although there are many clinical features suggestive of MODY diagnosis, there is no single clinical criterion. An online MODY Risk Calculator can be a useful tool for clinicians in the decision-making process for MODY genetic testing in some situations. Molecular genetic tests with a commercial gene panel should be performed in cases with a suspicion of MODY. Unresolved atypical cases can be further studied by exome or genome sequencing in a clinical or research setting, as available.

Maturity-onset diabetes of the young (MODY) are monogenic forms of diabetes characterized by autosomal dominant inheritance, early-onset diabetes (usually <25 years of age), preservation of endogenous insulin secretion with no signs of autoimmune process or insulin secretion[1,2]. In this review, we summarize the history of MODY, commonly encountered MODY forms, clinical characteristics of MODY, and practical tips from diagnosis to management.

HISTORY

In 1960, Dr Fajans presented mild asymptomatic diabetes occurring in non-obese children, adolescents, and young adults at the 1st International Congress of Endocrinology[1]. Professors Luft and Lundbaek commented on the non-existence of that kind of diabetes in Europe, citing their clinical experiences. Dr Fajans pointed out that such cases had been found after systematic testing of asymptomatic first-degree relatives of patients with diabetes, to which he was referring in his diabetes natural history study that he started in 1950s by screening asymptomatic family members. Five years later, Dr Fajans coined the term 'Maturity-onset type Diabetes of childhood or of the Young' for the first time to describe this unusual type of diabetes, during the 5th International Congress of Endocrinology in 1964. At that time, only two types of diabetes were known to the scientific community: Juvenile-onset type characterized by rapid insulin dependence and primarily seen in young people, and maturity-onset type characterized by mild diabetes phenotype that could usually be controlled by diet and oral agents occurring in middle-aged or older people. He chose this name to describe this unusual diabetes in young people because of its mild course similar to diabetes seen in adults. In 1974, Dr Tattersall and Dr Fajans confirmed the autosomal dominant mode of inheritance in this form of diabetes and they proposed the 'MODY' abbreviation for the first time, which was later adopted by the diabetes scientific community[3]. Molecular genetic etiologies of MODY forms were first discovered in the

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1990s starting with *GCK*-MODY (aka, MODY-2), *HNF1A*-MODY (aka, MODY-3), and *HNF4A*-MODY (aka, MODY-1)[4–9]. Since then, several other genes (at least 14) have been reported to cause diabetes with a MODY-like phenotype and while they been numbered from MODY-1 to MODY-14[10], the numbering systems have varied from author to author. Also, some of the forms listed among several forms have been disputed as causes of diabetes. Because of these problems and in anticipation that the number of genes associated with MODY will continue to increase, we and other experts in the field are now recommending naming forms of MODY with the associated gene name rather than a specific number (i.e., *GCK*-MODY instead of MODY-2)[11]. The MODY forms in relation to other types of diabetes mellitus are summarized in Figure 1.

MODY: PREVALENCE AND COMMON MODY FORMS

The prevalence of MODY is estimated as 1.1–6.5% of the pediatric diabetes population with a high degree of geographic variability that might arise from several factors in the criteria used to ascertain cases[12–16]. *GCK*-MODY, *HNF1A*-MODY, and *HNF4A*-MODY account for >90% of MODY cases with a genetic confirmation in several studies in the UK, Europe, and the USA. However, these three most common MODY types account for approximately <15% and 50% of clinically diagnosed MODY cases in adult Asians and MODY-type pediatric diabetes cases in Japanese children, respectively[17–19]. In Korean subjects with MODY and early-onset type 2 diabetes (n = 40), variants in *HNF1A* and *GCK* were found in 7.5% of the cohort implying the role of other yet-to-be determined genes in MODY in Asian populations[20]. About 50–90% of MODY cases are misdiagnosed as having type 1 diabetes or type 2 diabetes.

GCK-MODY is the most common type of MODY in some studies, characterized by non-progressive, mild hyperglycemia[2]. It is caused by a pathogenic variant in *GCK*, encoding the glucokinase gene, leading to a slightly higher set point for insulin secretion from the pancreas and for glucose production from the liver. It may also affect appetite due to its expression in the brain[21] and association with plasma ghrelin concentrations[22], but this hypothesis warrants further confirmation. Commonly, the affected parent may not have a diagnosis of diabetes, or has been misdiagnosed with type 2 diabetes. It is rarely associated with any actionable micro- or macrovascular complications of diabetes[23]. Although a large percentage of patients are unnecessarily treated with glucose lowering therapies prior to genetic diagnosis, it does not require treatment except in special circumstances (e.g., pregnancy)[24]. Hyperglycemia during pregnancy is associated with adverse outcomes including, but not limited to, fetal overgrowth and neonatal hypoglycemia[25]. If a fetus of the affected parent does not carry pathogenic *GCK*-variant, mild hyperglycemia in the mother can trigger excessive insulin production leading to excess fetal growth. In contrast, if a fetus of affected parent does have a pathogenic *GCK*-variant, fetal insulin secretion and fetal growth are expected to be normal due to similar set-points in both mother and fetus.

HNF1A-MODY is the most common form of MODY that results in familial symptomatic diabetes[2]. It is caused by a heterozygous pathogenic variant in *HNF1A*, which encodes a transcription factor (i.e., hepatocyte nuclear factor 1A) important in pancreatic differentiation and function. *HNF1A*-MODY usually presents during adolescence or young adulthood with initial post-prandial hyperglycemia followed by fasting hyperglycemia[26]. Because *HNF1A* is important for the expression of

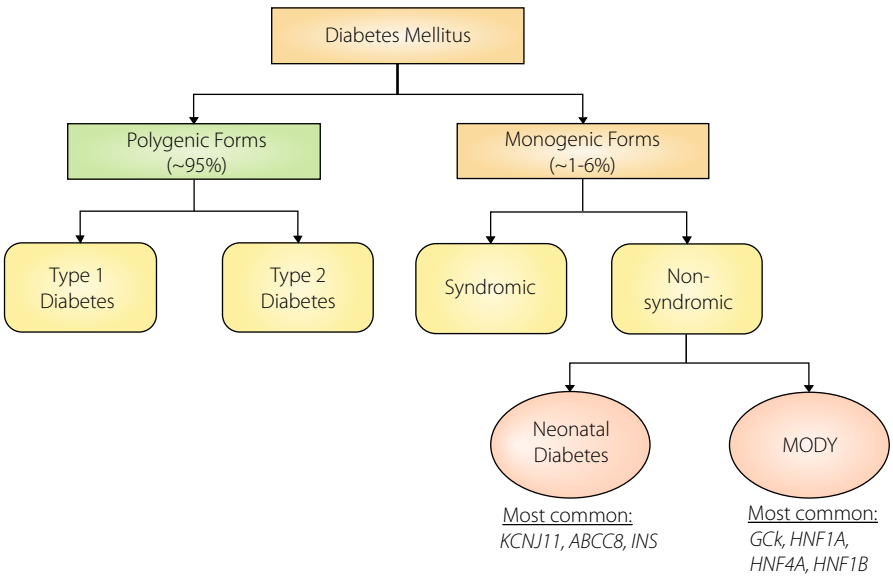

Figure 1 | Maturity-onset diabetes of the young in relation to different forms of diabetes mellitus.

SGLT2, critical for renal tubular reabsorption, these patients may have post-prandial glycosuria even before significant hyperglycemia[27]. The frequency of microvascular complications are highly dependent on glycemic control[28]. Treatment strategies mainly include diet and sulphonylureas as this type of MODY is very sensitive to sulphonylureas. Insulin treatment can be considered for some patients as a second line option[11]. Recent studies show emerging evidence for the usefulness of glucagon-like peptide-1 agonist and dipeptidyl peptidase-4 inhibitors in *HNF1A*-MODY[29–31]. However, SGLT2 inhibitors are cautioned against due to concern over further inhibition of remaining SGLT2 activity in the kidneys[11].

HNF4A-MODY is another form of familial symptomatic diabetes which occurs less frequently than *HNF1A*-MODY due to mutations and other perturbations of this related transcription factor[32]. It has similar clinical presentation and treatment responses to *HNF1A*-MODY. Fifteen percent of the cases have a history of neonatal hypoglycemia followed by diabetes later in life[33].

HNF1B-MODY is also known as renal cyst and diabetes syndrome (RCAD) caused by a heterozygous pathogenic variant or deletion in *HNF1B*[2,34]. The main presentation includes renal cyst/dysplasia first followed by diabetes during adolescence or young adulthood. In addition, the clinical spectrum may include pancreatic hypoplasia, exocrine pancreas deficiency, and genitourinary abnormalities[35]. Insulin is the first line treatment option for this type of MODY[11]. *De novo* genetic variants or deletions account for one-third to two-thirds of the cases and thus, a family history of diabetes in the first-degree relatives may not be present[34,36].

CLINICAL CHARACTERISTICS OF MODY CASES IN DIFFERENT POPULATIONS

Pihoker *et al.*[12] investigated the characteristics of MODY in the SEARCH for Diabetes in Youth Study, which is a multicenter observational study of youth with diabetes diagnosed at <20 years of age in the USA. Participants were selected for genetic testing for the three most common MODY types (*GCK*-, *HNF1A*-, and *HNF4A*-MODY) based on negative diabetes antibodies (glutamic acid decarboxylase-65 [GAD-65] and insulinoma associated antigen-2 [IA-2] antibodies), and fasting C-peptide level of 0.8 ng/mL or greater. Of 586 subjects, 47 (8%) of them tested positive for MODY. In MODY-positive cases, only 3 (6%) cases had a previous clinical MODY diagnosis and 50% were treated with insulin including one quarter of cases with *GCK*-MODY. Compared with the MODY-negative cases, the MODY-positive cases had a younger age at diagnosis (11.5 vs 13.3 years), lower BMI-z score (1.2 vs 1.8), and lower fasting C-peptide (2.2 vs 3.2 ng/mL). Interestingly, a similar percentage of individuals in both groups had a parental history of diabetes (50–51%) and acanthosis nigricans (40–61%).

The Progress in Diabetes Genetics in Youth (ProDiGY) Collaboration performed exome sequencing in 3,333 participants with a previous diagnosis of type 2 diabetes identified from SEARCH and TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) Studies[37]. Ninety-three (2.8%) participants tested positive for MODY, who had younger age at diagnosis (12.9 vs 13.6 years) and a lower C-peptide (3 vs 4.7 ng/mL) compared with the non-MODY group.

In a retrospective study of our racially/ethnically diverse population at Texas Children's Hospital (Houston, TX, USA), we screened our electronic medical record-based Diabetes Registry (n = 4,752) for likely MODY cases using the following three criteria: diagnosis of diabetes at <25 years of age, a family history of diabetes in three-consecutive generations, and absent islet antibodies except GAD-65[38]. Of those in the Diabetes Registry, 7.4% (n = 350) met the screening criteria. Baseline characteristics include mean age at diagnosis of 13 years, 62% female, 57% Hispanic, 26.4% non-Hispanic Black, and 13.8% non-Hispanic White. The frequency of previously assigned MODY diagnosis was 3.5 times higher in our study cohort compared with the entire registry (4.6% vs 1.3%). We then performed clustering analysis in the study cohort using variables commonly used to determine diabetes types (age, BMI-z, islet autoantibodies, hemoglobin A1c [HbA1c], C-peptide, glucose) resulting in four distinct clusters. The cluster with the highest rate of prior MODY diagnosis (25%) had the lowest age at diabetes diagnosis (10.9 years vs 13.8, 13.7, and 13.2 years), BMI-z score (0.5 vs 2.1, 2.4 and 2.4), C-peptide level (1.5 vs 2.3, 3.9 and 10.5), and acanthosis nigricans frequency (12.5% vs 73.4%, 80%, and 75%).

Based on the data from Swedish National Cohort Study, Carlsson *et al.*[39] suggested testing for MODY in patients with modestly raised glucose values with no islet autoantibodies. They studied 3,933 children and adolescents with diabetes to identify discriminatory characteristics at diabetes diagnosis for the three most common MODY types (*GCK*-, *HNF1A*-, and *HNF4A*-MODY). The detection rate increased from 1.2% to 49% with a good capture rate as investigators limited testing to autoantibody negative patients with HbA1c <7.5%. When MODY cases were compared with the entire cohort, discriminatory features for MODY diagnosis were negative islet autoantibodies (100% vs 11%), lower HbA1c (7% vs 10.7%), higher C-peptide (3 vs 1 ng/dL), absence of diabetic ketoacidosis (0% vs 15%), and a parental history of diabetes (63% vs 12%). It is important to note that characteristics of the entire cohort in this Swedish cohort are driven mainly by type 1 diabetes, in which the prevalence of type 2 diabetes in children is low. For populations with a higher prevalence of obesity and type 2 diabetes, the direction of some of these associations may change (e.g., requiring a C-peptide comparison 3–5 years after diagnosis).

Taken together, there is no single clinical criterion for a suspicion of MODY [2,12,40]. In a patient with a previous diagnosis of type 1 diabetes, negative islet antibodies, preserved beta-cell function, and low-insulin requirement beyond the partial remission phase and positive family history should raise suspicion for MODY. In contrast, in patients with type 2 diabetes, a lack of significant obesity and acanthosis, and the presence of a significant family history can be considered suspicious for MODY.

Such patients should also have antibody testing for type 1 diabetes. Also, the presence of typical syndromic characteristics of certain type of MODY (i.e., renal cyst/dysplasia for *HNF1B*-MODY; stable, non-progressive, mild hyperglycemia for *GCK*-MODY) should lead to specific genetic testing as well. As noted in earlier studies above, having obesity or acanthosis nigricans, or not having a family history of diabetes do not preclude a diagnosis of MODY.

The MODY Risk Calculator can be a helpful tool to select patients for MODY testing (https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator). This calculator has been developed and validated by the University of Exeter group in 1–35 year-old Caucasians for the three most common MODY types (*GCK*-, *HNF1A*-, and *HNF4A*-MODY)[41]. The calculator uses current age, age at diagnosis, sex, ethnicity, treatment regimen, BMI, HbA1c, parental history of diabetes, and the presence of certain medical problems associated with MODY phenotypes to calculate a post-test probability of MODY. The authors suggested >10% and >25% post-test probabilities should trigger genetic testing in patients who are and are not treated with insulin within 6 months of diagnosis, respectively. Although this is a helpful tool for many cases, clinicians should be cognizant about certain limitations of this MODY calculator. It was developed in Caucasians and its applicability to other races/ethnicities is yet to be determined. Although it was shown to perform well in Asians in a relatively small study including participants of mixed ethnic groups (Chinese, Malay, and Indian)[42], further investigation is warranted to better understand the efficacy of MODY calculator in Asians. The model was developed using the characteristics of the three most common MODY types, thus it may not be applicable to other MODY types. The model does not include islet autoantibody and C-peptide status, both of which can be very useful in selecting cases for MODY genetic testing.

CASE DISCUSSION

A 13-year-old Hispanic male presented with polyuria, polydipsia, and weight loss. His BMI was 22.7 kg/m^2 (87th percentile). He did not have acanthosis nigricans on physical examination. His HbA1c was 8.4% (reference range [RR]: <5.7%) and glucose was 232 mg/dL (RR for fasting: 70–99 mg/dL). He did not have diabetic ketoacidosis. He was suspected to have type 1 diabetes and started on multiple daily insulin injections. He tested negative for GAD-65, IA-2, zinc transporter-8 (ZnT8), and islet cell antibodies. His family history was significant for type 1 diabetes in the mother (diagnosed at age 10 years, treated with insulin) and the maternal grandfather (diagnosed in his 30s, treated with insulin and died at 69 years of age), and type 2 diabetes in the maternal uncle (diagnosed in his 30s, treated with tablets, and died of a heart attack at 38 years of age) and the maternal grandmother (diagnosed at 22 years of age, treated with metformin). The patient had a MODY genetic test done at Athena Diagnostics 5 months post-diagnosis, which revealed a heterozygous, pathogenic frameshift variant in *HNF1A* (C.872:1 bp duplication of C, Codon 291), consistent with *HNF1A*-MODY. At 8-months post-diagnosis, his treatment regimen was changed from multiple daily insulin injections to sulphonylurea treatment with an excellent response. At 15-months post-diagnosis, his HbA1c was 6% with an average glucose 148 mg/dL with 84% time-in-range over the preceding 7 days while only taking daily sulphonylurea tablet (2.5 mg daily). Of note, his test results raised the suspicion about misdiagnosis of some of the family members' diabetes types, and the mother was referred to her endocrinologist to get tested for *HNF1A*-MODY.

DIAGNOSTIC APPROACH

Patients with clinical features suggestive of MODY should undergo molecular genetic testing by next-generation sequencing with a MODY gene panel. Several MODY gene panels are available at commercial genetic laboratories. Awareness of the available options as well as their differences may help clinicians to choose the most appropriate panel. Table 1 provides a comparison of MODY gene panels of a few different genetic laboratories and a monogenic diabetes registry in the USA. The costs of MODY panels varies between $2,000 and 6,000 (personal

Table 1 | MODY/Monogenic diabetes panels in different genetic laboratories and a monogenic diabetes registry in the USA

Genetic Laboratory or Monogenic Diabetic Registry	Test name	Test code	Number of genes included	Availability of financial assistance
Athena Diagnostics	Monogenic Diabetes (MODY) Five Gene Evaluation[48]	885	5	Yes for qualified applicants
University of Chicago Clinical Genetics Laboratory	MODY Panel, NGS[49]	2,141	15 nuclear and 3 mitochondrial genes	
University of Chicago Monogenic Diabetes Registry[44]	Monogenic diabetes panel, NGS	N/A	>200	N/A (no charge if enrolled in a research study)
Baylor Genetics	MODY Panel by Massively Parallel Sequencing[50]	21,900	25	Yes for qualified applicants
Invitae	Monogenic Diabetes Panel[51]	55,001	28	Yes for qualified applicants

communication with genetic laboratories). However, many genetic laboratories have financial assistance programs for eligible patients, who can get a genetic test done at a much cheaper price or for free. For those patients who are not eligible for financial assistance and who cannot get insurance coverage for a genetic test, Invitae offers a monogenic diabetes panel at $250 for people who are interested in the self-pay option as at 2022. In the UK, the University of Exeter group can be helpful to explore options. Many countries are developing monogenic diabetes testing but availability and access varies widely.

If a commercial MODY panel is negative for a patient with suspected MODY, exome sequencing or genome sequencing may provide additional answers. One of us (MT) studied 10 children who were suspected to have MODY but had a negative MODY gene panel[10]. Exome sequencing in 10 probands and their parents revealed two new MODY cases in patients who were previously diagnosed with type 1 diabetes demonstrating the clinical utility of exome sequencing. Similarly, exome sequencing revealed three new MODY cases in 28 Asian patients with early-onset (<30 years) diabetes[43].

Although exome sequencing or genome sequencing may not be available in the clinical setting for the majority of patients, these services can be offered to eligible patients in research settings. For example, the RADIANT (The Rare and Atypical Diabetes Network) study is searching for new forms of atypical diabetes and for those who qualify, whole genome sequencing will be undertaken. RADIANT is a USA NIH-supported national consortium which aims to study atypical forms of diabetes (www.atypicaldiabetesnetwork.org), and patients with MODY phenotypes with no previously identified genetic etiology on a commercial gene panel may be eligible to enrol in RADIANT. Also, the University of Chicago Monogenic Diabetes Registry serves as a valuable source for patients suspected to have monogenic diabetes including MODY (www.monogenicdiabetes.uchicago.edu). This registry established in 2008, enrolled approximately 4,000 participants from 20 different countries with over 1,100 participants with known genetic cause of diabetes[44].

Identification of a genetic cause of diabetes in individuals with MODY forms has a significant impact on the daily lives of people with diabetes[45]. Having a genetic diagnosis leads to discontinuation of unnecessary treatment for some patients (i.e., individuals with *GCK*-MODY) and switching from injectable insulin treatment to convenient oral tablet with excellent glycemic control in others (i.e., individuals with *HNF1A*-MODY and *HNF4A*-MODY). Also, it guides clinicians to adjust the timeline and frequency of screening tests for diabetes complications because of the significantly different risk of complications across different MODY forms. With MODY forms already being excellent examples of the implementation of precision medicine in diabetes, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) established the Precision Medicine in Diabetes Initiative (PMDI) in 2018[46]. PMDI aims to leverage precision medicine for the diagnosis, prevention, treatment, prognosis, and monitoring of diabetes using an evidence based approach. The first consensus report by PMDI set the stage by identifying critical gaps in knowledge and evidence for the implementation of precision medicine in diabetes in these five key domains[47], which led to ongoing work to undertake systematic reviews in these areas by dedicated workgroups. The effort in this area is anticipated to result in development and implementation of evidence based clinical guidelines to practice precision medicine in diabetes.

CONCLUSIONS

Maturity-onset diabetes of the young forms are excellent examples of precision medicine in diabetes with variable clinical presentations and treatment responses. There are no uniform clinical criteria for MODY diagnosis, and high clinical suspicion is key for confirmation of genetic diagnosis. Available research opportunities can be leveraged for unresolved atypical cases.

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AUTHOR CONTRIBUTIONS

MT wrote the initial draft and edited the manuscript. LHP critically revised and edited the manuscript. All authors approved the final version of the manuscript.

DISCLOSURE

The authors have no conflict of interest to disclose.
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Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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