

# Clinical and Laboratory Characteristics of MODY Cases, Genetic Mutation Spectrum and Phenotype-genotype Relationship

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## What is already known on this topic?

Maturity onset diabetes of the young (MODY) is the term used to describe a group of inherited, non-autoimmune forms of diabetes mellitus. MODY diagnosis is often made at a young age (under 25 years of age), pancreatic autoantibodies are not present, there is a low insulin requirement, often a family history of autosomal dominant diabetes, no history of obesity and no history of diabetic ketoacidosis (DKA).

## What this study adds?

This large-series national study showed that the diagnostic criteria in the prediagnostic process of MODY should be reconsidered because some patients with genetically diagnosed MODY had a history of DKA, pancreatic antibody positivity and no family history of diabetes.

## Abstract

**Objective:** Maturity onset diabetes of the young (MODY) occurs due to mutations in genes involved in pancreatic beta cell function and insulin secretion, has heterogeneous clinical and laboratory features, and account for 1-5% of all diabetes cases. The prevalence and distribution of MODY subtypes vary between countries. The aim of this study was to evaluate the clinical and laboratory characteristics, mutation distribution, and phenotype-genotype relationship in a large case series of pediatric Turkish patients genetically diagnosed with MODY.

**Cite this article as:** Özsu E, Çetinkaya S, Bolu S, Hatipoğlu N, Savaş Erdeve Ş, Evliyaoğlu O, Baş F, Çayır A, Dündar İ, Akbaş ED, Uçaktürk SA, Berberoğlu M, Şıklar Z, Özalkak Ş, Muratoğlu Şahin N, Keskin M, Gül Şiraz Ü, Turan H, Öztürk AP, Mengen E, Sağsak E, Dursun F, Akyürek N, Odabaşı Güneş S, Aycan Z. Clinical and Laboratory Characteristics of MODY Cases, Genetic Mutation Spectrum and Phenotype-genotype Relationship. J Clin Res Pediatr Endocrinol. 2024;16(3):297-305



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**Conflict of interest:** None declared

**Received:** 18.12.2023

**Accepted:** 25.03.2024



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**Methods:** MODY cases from 14 different pediatric endocrinology departments were included. Diagnosis, treatment, follow-up data, and results of genetic analysis were evaluated.

**Results:** A total of 224 patients were included, of whom 101 (45%) were female, and the mean age at diagnosis was  $9.4 \pm 4.1$  years. Gene variant distribution was: 146 (65%) *GCK*; 43 (19%) *HNF1A*; 8 (3.6%) *HNF4A*, 8 (3.6%) *KLF11* and 7 (3.1%) *HNF1B*. The remaining 12 variants were: *PDX* (n = 1), *NEUROD1* (n = 3), *CEL* (n = 1), *INS* (n = 3), *ABCC8* (n = 3) and *KJNC11* (n = 1). Of the cases, 197 (87.9%) were diagnosed with incidental hyperglycemia, 16 with ketosis (7%) and 7 (3%) with diabetic ketoacidosis (DKA), while 30% presented with classical symptoms of diabetes. Two-hundred (89%) had a family history of diabetes. Anti-GAD antibody was detected in 13 cases, anti-islet antibody in eight and anti-insulin antibody in four. Obesity was present in 16. Distribution of therapy was: 158 (71%) diet only; 23 (11%) intensive insulin treatment; 17 (7.6%) sulfonylureas; 10 (4.5%) metformin; and 6 (2.7%) insulin and oral anti-diabetic treatment.

**Conclusion:** This was the largest genetically diagnosed series from Turkey. The most common gene variants were *GCK* and *HNF1A* with much lower proportions for other MODY types. Hyperglycemia was the most common presenting symptom while 11% of patients had diabetes-associated autoantibodies and 7% were obese. The majority of patients received dietary management only.

**Keywords:** Childhood, MODY, diagnosis

## Introduction

Maturity onset diabetes of the young (MODY) is the term used to describe a group of inherited, non-autoimmune forms of diabetes mellitus (DM). MODY was initially thought to be relatively rare but it has become apparent that it is more common than first thought. Despite increasing awareness of MODY, it has been estimated that up to 1-5% of MODY cases remain undiagnosed. Since the clinical spectrum is variable due to the range of genetic defects, there may be diagnostic delays, and some cases may not be diagnosed until adulthood. Furthermore, cases may sometimes be misdiagnosed as type 1 (T1DM) or type 2 DM (T2DM) (1,2,3).

Given the natural history of MODY, that there is cost-effective treatment, and the potential impact on more than one family member, it is essential to diagnose these cases correctly. The presence of family history, clinical and physical examination findings incompatible with T1DM or T2DM, and negative diabetes autoantibodies when present, strengthen the diagnosis of MODY (3). In addition, urinary c-peptide/creatinine ratio  $>0.2$  nmol/mmol has high specificity and sensitivity in differentiating MODY from T1DM (4).

Genetic testing is important for definitive diagnosis and identification of other family members with the same variant. Mutation analyses classify the type of MODY and this in turn informs about the expected clinical courses and guides treatment planning. In patients with *HNF4A* and *HNF1A* mutations, forms of MODY which are responsive to sulphonylurea therapy, it is important to change treatment regimens from insulin treatment, as low-dose sulphonylurea treatment may provide good glycemic control for years and, in patients with *GCK* mutations, will prevent unnecessary insulin treatment. Mutation screening is also important for asymptomatic relatives with a 50% risk of inheriting the mutation.

The distribution of MODY types differs between countries. Although *HNF1A* MODY is reported to be the most common type globally, there are countries where *GCK* MODY is observed more frequently (5). Therefore, knowing which of the MODY types is more common in one's own country is important. Determination of the MODY type will provide the most accurate approach for the pediatric endocrinologist to manage MODY patients. Moreover, managing clinicians should understand the phenotype-genotype relationship in MODY.

The aim of this study was to investigate the distribution of MODY types in a pediatric population from Turkey and to investigate the phenotype-genotype relationship.

## Methods

The study included pediatric patients with genetically diagnosed MODY from 14 pediatric endocrinology and diabetes departments in Turkey. Ethical approval was obtained from Ankara University Faculty of Medicine (decision number: 12-112-20, date: 13.02.2020). The National Pediatric Endocrinology and Diabetes Association (ÇEDD) supported the study. An electronic case registration form was created in the ÇEDD-NET data system of the association, and centers were asked to record their data using this system. The data entry took one year. Retrospective medical history (at least three generations of family history), clinical characteristics (age at diagnosis, year of diagnosis, duration of diabetes, presence of classical diabetes symptoms), laboratory results (blood glucose, insulin, c-peptide, glycated hemoglobin (HbA1c) levels, lipid profile, presence of acidosis at diagnosis, presence of autoantibodies at diagnosis, and reserve insulin values) and genetic data were transferred from electronic case record forms to Microsoft Excel (Microsoft Inc., Redmond, USA) and Statistical Package for the

Social Sciences (SPSS), version 20.0 (IBM Inc., Armonk, NY, USA) files for statistical evaluation.

Informed consent was obtained from the parents/guardians of the patient from all centers.

Patients with a positive family history in which at least two consecutive generations were affected, early-onset hyperglycemia, negative diabetes autoantibodies, and no classical features of T1DM or T2DM (not insulin-dependent or not requiring insulin treatment even after three years of insulin treatment, or having insulin reserve with serum c-peptide level >0.60 ng/mL) were sought from the clinics. Genetic analysis was performed with a presumptive prediagnosis of MODY. Patients had already had genetic analyses and they were genetically diagnosed.

Body mass index (BMI) values of the cases were evaluated according to the Neyzi et al. (6) data. adjusted for age and sex, and cases with BMI > 95<sup>th</sup> percentile were considered obese. Ketonemia was defined as a blood ketone level of 1 mg/dL, and diabetic ketoacidosis (DKA) was defined as a blood glucose level above 200 mg/dL with blood pH < 7.3 or HCO<sub>3</sub> < 15 mmol/L. Autoantibody status and reserve insulin values were recorded at diagnosis.

### Mutation Interpretation

Genetic analyses of the cases were performed by next-generation sequencing and screening for 14 currently known mutations. Each patient was included in the study with the genetic diagnosis of MODY being made in the unit where they were followed.

MODY DNA sequence analysis panel was performed on each patient. All results were assessed by genetic specialist according to ACGM classification. Results, which were pathogenic or likely pathogenic were accepted as positive (7).

### Statistical Analysis

Descriptive statistics were calculated for all patients taking part in the study using SPSS, version 21.0 (IBM Corp., Armonk, NY, USA). Data were expressed as the mean ± standard deviation (SD), median (minimum; maximum). The Kolmogorov-Smirnov test evaluated the normality of variables. Descriptive analyses are presented using means and SD for normally distributed variables. A p value <0.05 was assumed to indicate a statistically significant result in all analyses.

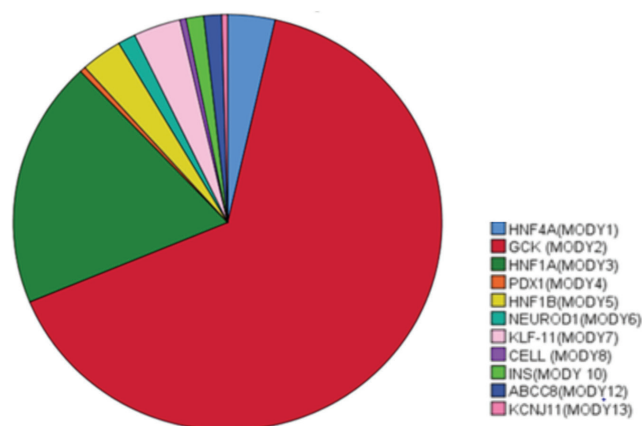
## Results

### General Features

A total of 224 cases were included in the study. Of these 101 (45%) were female, and the mean age at diagnosis was 9.4 ± 4.1 years and ranged widely from 0.2 to 17 years. On MODY genotyping, 146 (65%) cases were diagnosed as *GCK*, 43 (19%) cases were diagnosed as *HNF1A*, 8 (3.6%) cases were diagnosed as *HNF4A* and a further eight with *KLF11* while 7 (3.125%) patients had an *HNF1B* variant. In the remaining twelve cases there were three (1.3%) each with *NEUROD1*, *INS* and *ABCC8* mutations while the last three had *PDX* (n = 1), *CEL* (n = 1) and *KJNC11* (n = 1) mutations, respectively (Figure 1).

Most of the cases (n = 197, 87.9%) were diagnosed with incidental hyperglycemia, while 16 (7%) had ketosis and 7 (3%) had DKA; 30% had diabetes symptoms. There were 200 cases (89%) with a family history of DM; 93 (41%) had diabetes in two generations and 84 (37%) had diabetes in three generations. Relatives of 162 patients with diabetes were under the age of 40 years. In 24 patients, no family history was found. A proportion of the patients with genetically diagnosed MODY presented with T1DM-associated autoantibodies, including 13 (5.8%) with anti-GAD, 8 (3.6%) with anti-islet and 4 (1.8%) with anti-insulin antibodies. These cases were in *HNF4A*, *GCK*, *HNF1A*, *KLF11*, *KJNC11* MODY (type 1, 2, 3, 7, 12 MODY) types. Sixteen of the cases were obese. Clinical and laboratory characteristics of MODY types are given in Table 1.

While 158 (71%) of the patients were followed up with diet alone, 23 (11%) received intensive insulin therapy, 17 (7.6%) received sulfonylurea, 10 (4.5%) received metformin, and 6 (2.7%) received insulin and oral



**Figure 1.** Distribution of gene variants found in the 224 MODY cases from a Turkish pediatric population

antidiabetic therapy (Table 2a, 2b). Seven patients presented with DKA or developed DKA during follow-up and these patients' genotypes were: *HNF4A* (n = 2, 0.89%), *HNF1A* (n = 2, 0.89%), *HNF1B* (n = 1, 0.44%), *NEUROD1* (n = 1, 0.44%), and *ABCC8* (n = 1, 0.44%). The clinical and laboratory characteristics of the patients who presented with DKA are shown in Table 3. An *INS* gene mutation was found in one patient who developed DKA during follow-up.

The characteristics of patients receiving intensive insulin treatment are shown in Table 4. Insulin treatment was needed in 35 (15%) of the patients at diagnosis or follow-up. Of these patients, 13 (5%) had *HNF1A* and 6 (2%) had *HNF1B* MODY.

### Genotype-phenotype Characteristics and Treatment According to MODY Types

#### GCK MODY

*GCK* mutation was found in 146 (65%) of 224 patients. The mean ± SD age was 8.8 ± 3.9 years. Although all of the *GCK*

MODYs were diagnosed with incidental hyperglycemia, 23 of them had typical symptoms of T1DM. In 50% of the cases, there was a family history of diabetes in at least two generations. At the time of diagnosis, the mean blood glucose level was 125 ± 21 mg/dL, and c-peptide was 1.4 ± 1.3 mg/dL. HbA1c ranged from 5.4-10.2% with a mean of 6.3 ± 0.3%. Anti-GAD (n = 6), anti-insulin (n = 1) and islet cell antibodies (n = 5) were positive in some. Comorbidities included arachnoid cyst, short stature, asthma, cystic fibrosis, precocious puberty, connective tissue diseases, dyslipidaemia and undescended testis. While 135 patients were followed up with diet, six received oral anti-diabetic therapy, and five received intensive insulin treatment.

#### HNF1A MODY

Nearly a fifth (19.2%, n = 43) of the patients had this mutation. The mean ± SD age at diagnosis was 10.6 ± 4.3 years. Typical symptoms of T1DM were present in five patients, and 31 patients presented with incidental hyperglycemia. Thirty-five patients had a positive family

**Table 1. Demographic characteristics of pediatric genetically confirmed MODY cases in a Turkish cohort (n = 224)**

	<i>HNF4A</i> n = 8	<i>GCK</i> n = 146	<i>HNF1A</i> n = 43	<i>PDX1</i> n = 1	<i>HNF1B</i> n = 7	<i>NEUROD1</i> n = 3	<i>KLF-11</i> n = 8	<i>CEL</i> n = 1	<i>INS</i> n = 3	<i>ABCC8</i> n = 3	<i>KJNC11</i> n = 1	Mean
Age at diagnosis (years)	10.3 ± 4.6	8.8 ± 3.9	10.6 ± 4.3	3.9	12.4 ± 3	9 ± 7.8	11.1 ± 2	6	9.1 ± 2.3	10.5 ± 1.8	8.5	9.4 ± 4.1 (range 0.15-17)
Sex F/M	3/5	63/83	22/21	0/1	3/4	1/2	4/4	1/0	1/2	2/1	1	101/123 (45%/55%)
Symptom (+)	6	23	5	1	5	0	7	0	0	1	1	30% (49/224)
Symptom (-)	2	123	18	0	2	3	1	1	3	2	0	
Presentation (n)												
IH	5	145	31	0	5	2	3	1	3	3	1	197 (87%)
DK	1	0	9	0	1	0	3	0	1	1	0	16 (7%)
DKA	2	0	2	1	2	1	0	0	0	0	0	8 (3.5%)
Negative family history (n)	2	17	4	0	1	0	0	0	0	0	0	24/224 (11%)

F/M: female/male, IH: incidental hyperglycemia, DK: diabetic ketosis, DKA: diabetic ketoacidosis, MODY: maturity onset diabetes of the young

**Table 2a. Treatment**

	<i>PDX1</i> n = 1	<i>HNF1B</i> n = 7	<i>NEUROD1</i> n = 3	<i>KLF-11</i> n = 8	<i>CEL</i> n = 1	<i>INS</i> n = 3	<i>ABCC8</i> n = 3	<i>KJNC11</i> n = 1
Literature	D OAD (metformin, DPP4) Insulin	Insulin	D OAD Insulin	OAD Insulin	OAD Insulin	D OAD Insulin	OAD	Diet OAD Insulin
Treatment	D: 1	D: 1 intensive insuline: 4 Basal ins + OAD: 1	D: 2 Intensive ins: 1	D: 1 M: 1 Intensive ins: 4 Basal ins + OAD: 2	D: 1	D: 1 OAD: 1 Intensive ins: 1	OAD: 2	OAD: 1

OAD: oral anti-diabetic, M: metformin, DPP4: dipeptidyl peptidase-4 inhibitors, D: diet, ins: insuline

history. At diagnosis, mean blood glucose was  $209 \pm 162$  mg/dL, and c-peptide was  $1.5 \pm 0.96$  ng/mL. Mean HbA1c was  $8.8 \pm 3.1$  %. Ten patients had autoantibody positivity. Comorbidities included exudative retinopathy (n = 2), asthma (n = 1), growth hormone deficiency (n = 1), celiac

disease (n = 1), pelviectasis (n = 1), hearing loss (n = 2), and sensory neuropathy (n = 1). Thirteen of the patients were on diet therapy, 15 were on oral anti-diabetic therapy and nine were on insulin therapy.

**Table 2b. Treatment**

Treatment	<i>HNF4A</i> n = 8	<i>GCK</i> n = 146	<i>HNF1A</i> n = 43
Lecture	Diet SU GLP-1 RA Insulin	Diet	SU Meglitinide, GLP-1 RA, SGLT-2 Insulin
In our cases	D: 4 SU: 2 Intensive ins: 2	D: 135 SU: 3 OAD (M): 3 Insulin: 2 Intensive ins: 3	D: 13 OAD (S): 11 OAD (M): 4 ins: 7 Basal ins + OAD: 2

OAD: oral anti-diabetic, M: metformin, D: diet, SU: sulphonylureas, GLP-1 RA: glucagon-like peptide 1 receptor agonist, SGLT-2: sodium-glucose transport protein 2 inhibitors, ins: insuline

**Table 3. Characteristics of patients presenting with acidosis or developing acidosis during follow-up**

	<i>HNF4A</i> -MODY n = 2		<i>HNF1A</i> -MODY n = 2		<i>HNF1B</i> -MODY n = 1	<i>NEUROD1</i> - MODY n = 1	<i>INS</i> -MODY n = 1
Sex	M	M	M	F	M	F	F
Age of diagnosis, years	8.2	10	12	15	15	18	16.6
GAD	Negative	Negative	Negative	Negative	Negative	Negative	Negative
ICA	No data	Negative	Negative	<b>Positive</b>	Negative	Negative	Negative
Anti insulin	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Family history	No	No	Yes (grandfather)	Yes (brother, grandmother, grandfather)	Yes (father)	Yes (father uncle, aunt)	Yes Father
Glucose at Dx (mg/dL)	674	548	443	210	600	281	269
C-peptide (ng/mL)	0.60	0.53	0.1	0.1	0.1	0.1	3.47
HbA1c (%)	11.78	10.6	13.2	9	8	7.5	11.2
Treatment	Int insulin the same treatment continued	Int insulin after diet	Int insulin the same treatment continued	Int insulin the same treatment continued	Int insulin the same treatment continued	Int insulin the same treatment continued	Int insulin the same treatment continued

F: female, M: male, HbA1c: glycated hemoglobin, int: initially, MODY: maturity onset diabetes of the young

**Table 4. Characteristics of patients on insulin**

	<i>HNF4A</i>	<i>GCK</i>	<i>HNF1A</i>	<i>HNF1B</i>	<i>NEUROD1</i>	<i>KLF-11</i>	<i>INS</i>	<i>ABCC8</i>	Total
Number of patients	2	5	13	6	1	6	1	1	35
Features at presentation	K: 1 DKA: 1 DM	K: 0 DKA: 0 Diabet	K: 5 DKA: 2 Diabet	K: 1 DKA: 2 Diabet	K: 1 DKA: 1 Diabet	K: 3 DKA: 0 Diabet	K: 0 DKA: 0 Diabet	K: 0 DKA: 0 Diabet	
symptom at diagnose:	2	2	5	6	1	6	0	0	
HbA1c %	11.7, 12.9	5.8, 6, 6.4, 7.2, 7.4	6, 7, 7.4, 8, 8.4, 8.8, 9, 11.30, 12.5, 13.6, 14.6, 20	6, 7.5, 7.7, 8, 9.5, 17.5	7.4	6.8, 9.8, 10, 11.9, 14.7, 15.6	11.2	5.8	

K: ketosis, DKA: diabetic ketoacidosis, F: female, M: male, HbA1c: glycated hemoglobin, DM: diabetes mellitus



### **HNF4A MODY**

This MODY subtype constituted 3.5% (n = 8) of the cases. The mean age at diagnosis was  $10.3 \pm 4.6$  years. There was one case with a birth weight of over 4000 g. Five cases had incidental hyperglycemia, and six cases had typical symptoms of diabetes. Acidosis was present in two cases, and autoantibody positivity was observed in one case. At the time of diagnosis, mean blood glucose was  $306 \pm 216$  mg/dL, and c-peptide was  $1.9 \pm 1.2$  ng/mL. while HbA1c range was 4.7-11.7%. One patient was obese at diagnosis. The only comorbidity was spinocerebellar syndrome (n = 3). While four of the patients were being managed with the diet, two were being treated with oral anti-diabetic therapy and two were being treated with insulin.

### **HNF1B MODY**

This mutation was detected in 3.1% (n = 7) of the cases. The mean age at diagnosis was  $12.4 \pm 3$  years. Five patients had incidental hyperglycemia, and five patients had symptoms of diabetes. Two patients presented with DKA. Six patients had a family history. At the time of diagnosis, blood glucose was  $308 \pm 177$  mg/dL, and c-peptide was  $1.18 \pm 1.0$  ng/mL. HbA1c range was 5.4-14.5%. No autoantibody positivity was found in any of the patients. Additional anomalies were chronic renal failure and elevated transaminases in one, focal segmental glomerulosclerosis in polycystic kidney in two, and renal cyst in one. Four of the patients were receiving insulin, one was on diet only and one was receiving oral anti-diabetic therapy and basal insulin.

### **KLF MODY**

*KLF* MODY was present in 3.5% (n = 8) of the patients. The mean age at diagnosis was  $11.2 \pm 2.0$  years. Three patients presented with incidental hyperglycemia, seven had symptoms of diabetes and three patients with diabetic ketosis. Family history was present in all cases. At diagnosis, blood glucose was  $278 \pm 175$  mg/dL, and c-peptide was  $2.2 \pm 2.0$  ng/mL. The range of HbA1c was 5.6-10.2%. Only one patient had autoantibodies (anti-GAD). One patient was on a diet, one on oral anti-diabetic therapy, two on oral anti-diabetic therapy and basal insulin, and four on intensive insulin treatment.

### **NEUROD1 MODY**

*NEUROD1* MODY was found in 1.3% (n = 3) of the cases. Their age was 1, 12 and 15 years old and one patient presented with DKA. No autoantibody positivity was detected. Additional anomalies included epilepsy in one patient and mental motor retardation (MMR) in one. At diagnosis, blood glucose was  $164 \pm 100$  mg/dL and c-peptide

was  $0.8 \pm 0.7$  mg/dL. HbA1c was in the range of 5.5-8%. Family history was not found in any patient. Two patients were on a diet, and one received intensive insulin treatment.

### **INS MODY**

This MODY subtype was found in 1.3% (n = 3) cases. Their ages were 7.5, 7.8 and 11 years old. Two patients had no symptoms of diabetes, and one patient presented with DKA. All three patients had a family history. Acidosis developed in one patient during follow-up. No autoantibody positivity was detected. At the time of diagnosis, blood glucose was  $200 \pm 64$  mg/dL, and c-peptide was  $8.5 \pm 4.3$  mg/dL. HbA1c ranged from 6.2 to 14%. MMR was associated with one patient. One patient was on a diet, and two were receiving intensive insulin.

### **ABCC8 MODY**

This subtype of MODY was found in 1.3% (n = 3) of the cases. Their age was 8.5, 11 and 12 years and diabetes symptoms were absent in two. Family history was present in all patients, and one patient was positive for autoantibodies. At diagnosis, blood glucose was  $140 \pm 26$  mg/dL, and c-peptide was  $2.4 \pm 0.58$  mg/dL. Two of the patients were taking oral anti-diabetic therapy and the other was managed with diet.

### **PDX MODY**

A 3.9-year-old patient presented with DKA. Family history was positive. No autoantibodies were detected. Admission HbA1c was 5.2%. Blood glucose was 135 mg/dL, and c-peptide was 3.4 mg/dL at the time of diagnosis. He was being managed with diet only.

### **CEL MODY**

*CEL* variant associated MODY was detected in one patient, 6 years old, who presented with incidental hyperglycemia. There was no family history. Insulin was not started during the follow-up. Autoantibodies were negative and HbA1c was 5.6%. At diagnosis, blood glucose was 137 mg/dL, and c-peptide was 0.7 mg/dL. He was managed with diet only.

### **KJNC11 MODY**

This form of MODY was detected in one case who was 8.5 years old. Symptoms of diabetes and autoantibody positivity were present at presentation. There was a family history of diabetes. HbA1c was 7.8%, and insulin was not started during follow-up. At the time of diagnosis, blood glucose was 191 mg/dL, and c-peptide was 2.1 mg/dL. The patient was followed up with oral anti-diabetic therapy.

Of the 224 patients evaluated, eight patients presented with acidosis. These cases were limited to the MODY

**Table 5. Cases with autoantibody positivity**

	<i>HNF4A</i> n = 8	<i>GCK</i> n = 146	<i>HNF1A</i> n = 43	<i>PDX1</i> n = 1	<i>HNF1B</i> n = 7	<i>NEUROD1</i> n = 3	<i>KLF-11</i> n = 8	<i>CELL</i> n = 1	<i>INS</i> n = 3	<i>ABCC8</i> n = 3	<i>KJNC11</i> n = 1	Total
<b>Anti-GAD</b>	Anti-GAD: 1	Anti-GAD: 6	Anti-GAD: 4	Anti-GAD: 0	Anti-GAD: 0	Anti-GAD: 0	Anti-GAD: 1	Anti-GAD: 0	Anti-GAD: 0	Anti-GAD: 0	Anti-GAD: 0	13
<b>Anti-insulin</b>	Anti-insulin: 0	Anti-insulin: 1	Anti-insulin: 3	Anti-insulin: 0	Anti-insulin: 0	Anti-insulin: 0	Anti-insulin: 0	Anti-insulin: 0	Anti-insulin: 0	Anti-insulin: 0	Anti-insulin: 0	8
<b>Anti-islet</b>	Anti-islet: 0	Anti-islet: 5	Anti-islet: 3	Anti-islet: 0	Anti-islet: 0	Anti-islet: 0	Anti-islet: 0	Anti-islet: 0	Anti-islet: 0	Anti-islet: 0	Anti-islet: 0	0
	1	12	10	0	0	0	1	0	0	1	0	25

types 1, 3, 5, and 6 and their detailed characteristics are shown in Table 3. DKA developed in one patient with *INS* mutation during follow-up. Table 5 shows the characteristics of the patients with positive autoantibodies.

## Discussion

In this study, which is the largest genetically diagnosed series from Turkey, the most common form of MODY was *GCK*-MODY (65%) followed by *HNF1A*-MODY (19%), while the other types were much rarer. Although the majority of cases were diagnosed because of incidental hyperglycemia, there were also cases with DKA and ketosis without a family history. Obesity was rarely associated with MODY, while comorbidities were seen in some MODY types.

MODY is reported with different frequencies depending on the ethnicity, selected patient population, number of genes analyzed and technical characteristics. The distribution of subgroups may also differ according to the method, environment, and technique. In the present study, which presents a representation of several centers from across Turkey, MODY2 (*GCK*-MODY) was the most common diagnosis, as reported previously (7,8). While *GCK* mutations were found incidentally, as expected, diabetes symptoms were observed in patients with *HNF1A* and *HNF4A* variants. Treatment was changed in 37 (16%) of our patients after genetic diagnosis or during follow-up (5,7,8,9,10,11).

In the largest series from Germany/Austria, MODY1 was found in 44, MODY2 in 609, MODY3 in 230, and MODY5 in 35 of 1047 MODY cases from 76,836 children under 20 years of age with diabetes (12). In the UK, MODY prevalence and subtype studies have been performed extensively and it has been reported that *HNF1A*-MODY is the most common type (52%) with *GCK*-MODY the second most common. While MODY due to *HNF1A* mutation is most common in European countries (13), *GCK*-MODY is the most common type in Japan, although there are few studies from Asian and Far Eastern countries (14).

Studies from Italy have shown that the selected patient population is important in determining the frequency of the MODY subtype. In the MODY subgroup in which patients with symptomatic hyperglycemia were evaluated, *HNF1A*- and *HNF1B*-MODY were most prevalent, while in the group with incidental hyperglycemia, *GCK*-MODY was most common. This is also a factor in the difference in frequency of MODY subtypes in adult and pediatric studies. For an accurate ranking, both age groups should be evaluated together (15).

Family history has been used as an essential criterion in MODY probability calculation models. This probability calculation reduces the probability of MODY in the absence of family history, but case reports and the present series show that there may be some exceptional cases. In a large series reported from Japan, 18% of the cases with genetically proven MODY did not have a family history (14). Furthermore, novel mutation was demonstrated in 7.3% of patients with the four most common MODY subtypes reported from Slovakia (16). In our series, the *de novo* mutation rate was 11%.

The use of anti-GAD positivity as a criterion for exclusion of MODY is a matter of debate. In a large series, anti-GAD was found to be positive in only 5 of 508 MODY cases, and this rate was similar to the normal population rate. However, in a Czech study, anti-GAD positivity was found in 7 of 28 MODY cases, and IAC2 positivity was found in one of 28 MODY cases. In these patients, the course of diabetes was worse, and HbA1c values were higher. Autoantibody negativity has been reported with appropriate therapeutic control of diabetes. Schober et al. (17) found a positive autoantibody rate of 17% in a German-Austrian series (18,19). In the present study, autoantibodies were positive in 25 patients. This may be due to a condition termed “double diabetes”. Polygenic diabetes has been reported to affect 3-4% of MODY cases, and the coexistence of T2DM and MODY is more common than T1DM and MODY (20). In the present series, only three patients with *GCK* mutation had increased HbA1c values and insulin requirement during follow-up. In a

Polish study, increased HbA1c values were also reported in patients with *GCK* mutation. This was explained by T1DM or T2DM accompanying monogenic diabetes. Thus, monogenic DM does not preclude the existence of other types. In 8 of 285 cases with *GCK* mutation, HbA1c values above 7.5% were reported. Steele et al. (21) also found HbA1c values between 8.2-9.5% in 6 of 235 cases with *GCK* mutation.

Although obesity is used to differentiate cases with T2DM from MODY, obesity associated with rare types of MODY, such as those caused by variants in *IPF1/PDX1* (MODY 4), *NEUROD1* (MODY 6), *BLK* (MODY 11) and *ABCC8* (MODY 12), and even common types (*HNF1A*- and *HNF4A*-MODY) have been reported in recent years. Therefore, obesity in MODY may be more common than previously thought, probably due to the general increase in global obesity prevalence (14). In the present series, obesity was found in 16 (7%) cases at diagnosis. In a Japanese study, the rate of overweight was 8.2%, and insulin resistance was 22% (21).

While MODY due to variants in *HNF4A*, *HNF1A* and *HNF1B* may present with DKA, *INS*, *NEUROD1* and *PDX*, which are rare types, may also present with DKA (20). Consistent with the literature, our patients also had these mutations and presented with acidosis due to insulin deficiency. It seems that using acidosis as an exclusion criterion for MODY may exclude some cases.

The criteria of three generations affected with diabetes, autoantibodies being negative, and insulin reserve present do not always hold true. In the present series, autoantibodies were positive in 25 patients, seven patients presented with DKA, and no family history was found in 24 patients. Approximately 50% of positive MODY cases do not fulfill the classical MODY diagnostic criteria; some patients with genetically confirmed MODY may also have pancreatic antibodies, and some *de novo* mutations may have occurred (21).

Over time and with more extensive research, knowledge of the natural history of MODY has increased. The ability to partially or completely change the treatment of people diagnosed with MODY from insulin to oral hypoglycaemic agents has saved patients from injections and unnecessary insulin therapy. However, while *GCK* mutations are followed up only with diet, *PDX*, *INS*, *BLK* and *APPL1* variant-associated MODY cases require early insulin, and, *HNF4A*, *HNF1A* and *PAX4* defects may also require oral antidiabetic or insulin. MODY due to *ABCC8* and *KCNJ11* mutations respond well to oral antidiabetics. In *HNF1B*, *NEUROD1*, *KLF11* and *CEL* mutations, the response to

oral antidiabetics is variable and insulin requirement develops over time (22). In our series, treatment changes were made in 37 patients during follow-up. While 71% of the patients were followed up only by adjusting their diet, 10% were receiving intensive insulin treatment, and 7% were receiving sulfonylurea.

Strengths of the present study include the high number of cases compared to early studies from Turkey, the detailed information about clinical characteristics of the identified cases and that this was a nationally supported study.

### Study Limitations

However, the limitations include the fact that not all centers participated, the MODY panels used varied from center to center and the interpretation of the MODY reports were performed by several geneticists.

### Conclusion

This large-series national study showed that the diagnostic criteria in the prediagnostic process of MODY should be reconsidered in the presence of DKA, the presence of antibody positivity and the absence of family history in patients with genetically diagnosed MODY in the Turkish population. Therefore, it does not seem appropriate to use obesity and/or the absence of DKA as absolute criteria for suggesting that a patient does not have MODY, and this will need to be considered in the development of updated MODY screening guidelines.

### Acknowledgements

The authors thank the children and parents for participating in the study. The authors thank to Jeremy Jones for editing.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from Ankara University Faculty of Medicine (decision number: 12-112-20, date: 13.02.2020).

**Informed Consent:** Informed consent was obtained from the parents/guardians of the patient from all centers.

### Authorship Contributions

Concept: Elif Özsu, Zehra Aycan, Merih Berberoğlu, Zeynep Şıklar, Design: Elif Özsu, Zehra Aycan, Zeynep Şıklar, Data Collection or Processing: Elif Özsu, Semra Çetinkaya, Semih Bolu, Nihal Hatipoğlu, Şenay Savaş Erdeve, Olcay Evliyaoğlu, Firdevs Baş, Atilla Çayır, İsmail Dündar, Emine Demet Akbaş, Seyid Ahmet Uçaktürk, Merih Berberoğlu, Zeynep Şıklar, Şervan Özalkak, Nursel Muratoğlu Şahin, Melikşah Keskin, Ülkü Gül Şiraz, Hande Turan, Ayşe Pınar



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**Financial Disclosure:** The authors declared that this study received no financial support.

## References

1. Tattersall RB. Mild familial diabetes with dominant inheritance. *Q J Med.* 1974;43:339-357.
2. Shields B, Colclough K. Towards a systematic nationwide screening strategy for MODY. *Diabetologia.* 2017;60:609-612. Epub 2017 Jan 29
3. Irgens HU, Molnes J, Johansson BB, Ringdal M, Skriverhaug T, Undlien DE, Søvik O, Joner G, Molven A, Njølstad PR. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. *Diabetologia.* 2013;56:1512-1519. Epub 2013 Apr 27
4. Özsu E, Cizmecioglu FM, Yesiltepe Mutlu G, Yuksel AB, Caliskan M, Yesilyurt A, Hatun S. Maturity Onset Diabetes of the Young due to Glucokinase, HNF1-A, HNF1-B, and HNF4-A Mutations in a Cohort of Turkish Children Diagnosed as Type 1 Diabetes Mellitus. *Horm Res Paediatr.* 2018;90:257-265. Epub 2018 Nov 27
5. Gökşen D, Yeşilkaya E, Özen S, Kor Y, Eren E, Korkmaz Ö, Berberoğlu M, Karagüzel G, Er E, Abacı A, Evliyaoglu O, Akbaş ED, Ünal E, Bolu S, Nalbantoğlu Ö, Anık A, Tayfun M, Büyükinan M, Abalı S, Can Yılmaz G, Kor D, Söbü E, Şıklar Z, Polat R, Darcan Ş. Molecular Diagnosis of Monogenic Diabetes and Their Clinical/Laboratory Features in Turkish Children. *J Clin Res Pediatr Endocrinol.* 2021;13:433-438. Epub 2021 Jul 8
6. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. *J Clin Res Pediatr Endocrinol.* 2015;7:280-293.
7. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405-424. Epub 2015 Mar 5
8. Özdemir TR, Kırbıyık Ö, Dündar BN, Abacı A, Kaya ÖÖ, Çatlı G, Özyılmaz B, Acar S, Koç A, Güvenç MS, Kutbay YB, Erdoğan KM. Targeted next generation sequencing in patients with maturity-onset diabetes of the young (MODY). *J Pediatr Endocrinol Metab.* 2018;31:1295-1304.
9. Haliloglu B, Hysenaj G, Atay Z, Guran T, Abalı S, Turan S, Bereket A, Ellard S. GCK gene mutations are a common cause of childhood-onset MODY (maturity-onset diabetes of the young) in Turkey. *Clin Endocrinol (Oxf).* 2016;85:393-399. Epub 2016 Jul 5
10. Ağıladioğlu SY, Aycan Z, Çetinkaya S, Baş VN, Önder A, Peltek Kendirci HN, Doğan H, Ceylaner S. Maturity onset diabetes of youth (MODY) in Turkish children: sequence analysis of 11 causative genes by next generation sequencing. *J Pediatr Endocrinol Metab.* 2016;29:487-496.
11. Karaoglan M, Nacarkahya G. Clinical and laboratory clues of maturity-onset diabetes of the young and determination of association with molecular diagnosis. *J Diabetes.* 2021;13:154-163. Epub 2020 Oct 2
12. Warncke K, Kummer S, Raile K, Grulich-Henn J, Woelfle J, Steichen E, Prinz N, Holl RW. Frequency and Characteristics of MODY 1 (HNF4A Mutation) and MODY 5 (HNF1B Mutation): Analysis From the DPV Database. *J Clin Endocrinol Metab.* 2019;104:845-855.
13. Nkonge KM, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). *Clin Diabetes Endocrinol.* 2020;6:20.
14. Yorifuji T, Higuchi S, Kawakita R, Hosokawa Y, Aoyama T, Murakami A, Kawae Y, Hatake K, Nagasaka H, Tamagawa N. Genetic basis of early-onset, maturity-onset diabetes of the young-like diabetes in Japan and features of patients without mutations in the major MODY genes: Dominance of maternal inheritance. *Pediatr Diabetes.* 2018;19:1164-1172. Epub 2018 Jul 1
15. Lorini R, Klersy C, d'Annunzio G, Massa O, Minuto N, Iafusco D, Bellannè-Chantelot C, Frongia AP, Toni S, Meschi F, Cerutti F, Barbetti F; Italian Society of Pediatric Endocrinology and Diabetology (ISPED) Study Group. Maturity-onset diabetes of the young in children with incidental hyperglycemia: a multicenter Italian study of 172 families. *Diabetes Care.* 2009;32:1864-1866. Epub 2009 Jun 29
16. Stanik J, Dusatkova P, Cinek O, Valentinova L, Huckova M, Skopkova M, Dusatkova L, Stanikova D, Pura M, Klimes I, Lebl J, Gasperikova D, Pruhova S. De novo mutations of GCK, HNF1A and HNF4A may be more frequent in MODY than previously assumed. *Diabetologia.* 2014;57:480-484. Epub 2013 Dec 10
17. Schober E, Rami B, Grabert M, Thon A, Kapellen T, Reinehr T, Holl RW; DPV-Wiss Initiative of the German Working Group for Paediatric Diabetology and. Phenotypical aspects of maturity-onset diabetes of the young (MODY diabetes) in comparison with Type 2 diabetes mellitus (T2DM) in children and adolescents: experience from a large multicentre database. *Diabet Med.* 2009;26:466-473.
18. McDonald TJ, Colclough K, Brown R, Shields B, Shepherd M, Bingley P, Williams A, Hattersley AT, Ellard S. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. *Diabet Med.* 2011;28:1028-1033.
19. Urbanová J, Rypáková B, Procházková Z, Kučera P, Cerná M, Anděl M, Heneberg P. Positivity for islet cell autoantibodies in patients with monogenic diabetes is associated with later diabetes onset and higher HbA1c level. *Diabet Med.* 2014;31:466-471. Epub 2013 Oct 16
20. Fendler W, Małachowska B, Baranowska-Jazwiecka A, Borowiec M, Wyka K, Malecki MT, Jarosz-Chobot P, Mysliwiec M, Mlynarski W; PolPeDiab Study Group. Population-based estimates for double diabetes amongst people with glucokinase monogenic diabetes, GCK-MODY. *Diabet Med.* 2014;31:881-883.
21. Steele AM, Wensley KJ, Ellard S, Murphy R, Shepherd M, Colclough K, Hattersley AT, Shields BM. Use of HbA1c in the identification of patients with hyperglycaemia caused by a glucokinase mutation: observational case control studies. *PLoS One.* 2013;8:e65326.
22. Aarthy R, Aston-Mourney K, Mikocka-Walus A, Radha V, Amutha A, Anjana RM, Unnikrishnan R, Mohan V. Clinical features, complications and treatment of rarer forms of maturity-onset diabetes of the young (MODY) - A review. *J Diabetes Complications.* 2021;35:107640. Epub 2020 May 29