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Genotype, Phenotype, and Clinical Characteristics of Maturity-Onset Diabetes of the Young (MODY): Predominance of *GCK*-MODY

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What is already known on this topic?

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes mellitus. To date, 14 different genes associated with MODY have been reported: hepatocyte nuclear factor-4-alpha; glucokinase; hepatocyte nuclear factor-1-alpha; pancreas-duodenum homeobox protein-1; hepatocyte nuclear factor-1 beta; neuronal differentiation-1; Kruppel-like factor 11; carboxyl ester lipase; paired box-4; insulin (*INS*); B lymphocyte kinase; ATP-binding cassette subfamily C member 8; potassium channel, inwardly rectifying, subfamily J member 11; and adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1. The diagnosis of MODY includes dominant inheritance with at least two (preferably three) consecutive affected generations; onset of diabetes is typically before the age of 25-30 years, there is evidence of significant but impaired residual insulin secretion reflected in c-peptide levels, and tests for autoantibodies associated with type 1 diabetes mellitus are negative in most cases (very rare exceptions have been reported). Stable, mild, non-progressive hyperglycemia is suggestive of glucokinase (*GCK*)-MODY in asymptomatic individuals.

What this study adds?

As in various studies conducted in children from Türkiye, the most frequently detected MODY type in our cohort was *GCK*-MODY. Although MODY is generally known as an autoantibody-negative type of diabetes, with islet cell antibody being particularly unusual, autoantibody positivity was detected in approximately one-quarter of the cases in our study and more than half of these were anti-islet cell antibodies.

Abstract

Objective: Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes characterised by early-onset diabetes and inherited in an autosomal dominant manner. MODY results from heterozygous mutations in genes important for pancreatic β-cell development or function. The objective was to identify the most common and rarest types of MODY amongst our cases with genetically confirmed MODY diagnosis, to evaluate clinical and laboratory features and treatment regimens.

Methods: The epidemiological, auxological, and laboratory data, genetic analysis results and treatment regimens of patients diagnosed with MODY were retrospectively evaluated.

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Results: Of the 44 cases included, 27 (61.4%) were male and the median age at diagnosis was 10.07 (1-16.8) years. There was a family history of diabetes in 42 (95.5%) cases. The distribution of gene variants was: 25 (55.8%) glucokinase (*GCK*), 4 (9.1%) hepatocyte nuclear factor-4-alpha, 4 (9.1%) carboxyl ester lipase, 2 (4.5%) B lymphocyte kinase, 4 (9.1%) ATP-binding cassette subfamily C member 8, 2 (4.5%) Kruppel-like factor 11, 1 (2.3%) insulin (*INS*), 1 (2.3%) potassium channel, inwardly rectifying, subfamily J member 11, and 1 (2.3%) adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1. At presentation, 23 (52.3%) of the cases had incidental hyperglycemia while 14 (31.8%) had polyuria and polydipsia. Diabetic ketoacidosis was detected in 4 (9.1%) and ketonemia in 3 (6.9%). At least one of the diabetes autoantibodies (anti-glutamate acid decarboxylase, anti-islet cell antibodies, anti-insulin autoantibodies) was detected in 11 (25%) cases, of which 7/11 were islet antibodies, and 5 patients (11%) had two autoantibodies positive simultaneously. In terms of treatment, 26 (59%) received diet and lifestyle changes only, 18 (41%) received oral antidiabetic agents and/or insulin, and 6 (13.6%) received both oral antidiabetic agents and insulin.
Conclusion: The most common type of MODY in our cohort was *GCK*-MODY. Although MODY is generally known as an autoantibody-negative type of diabetes, autoantibody positivity was detected in 11 of 44 cases (25%) in the present study.
Keywords: MODY, diabetes autoantibodies, childhood

Introduction

Maturity-onset diabetes of the young (MODY) represents the most prevalent form of monogenic diabetes, resulting from defects in a single gene or chromosomal locus. All currently identified MODY subtypes are attributed to dominant heterozygous mutations in genes that are pivotal for the development or function of pancreatic β-cells (1).

A total of 14 different genes have been identified as being associated with mutations that are linked to MODY. Of these, six encode key factors. The genes in question are: hepatocyte nuclear factor-4-alpha (*HNF4α*); glucokinase (*GCK*); hepatocyte nuclear factor-1-alpha (*HNF1α*); pancreas-duodenum homeobox protein-1 (*PDX1*); hepatocyte nuclear factor-1 beta (*HNF1β*); and neuronal differentiation-1 (*NEUROD1*). The following genes have been identified as being associated with MODY: Kruppel-like factor 11 (*KLF11*); carboxyl ester lipase (*CEL*); paired box-4 (*PAX4*); insulin (*INS*); B lymphocyte kinase (*BLK*); adenosine triphosphate (ATP)-binding cassette subfamily C member 8 (*ABCC8*); potassium channel, inwardly rectifying, subfamily J member 11 (*KCNJ11*); and adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1 (*APPL1*) (2).

The classic MODY phenotype is characterized by the absence of ketosis and the absence of insulin dependence, with a diagnosis of diabetes occurring before the age of 25 years. In addition, there must be a family history of at least one affected individual. These criteria are employed to define the MODY phenotype and to identify patients who may be suitable candidates for genetic testing (3,4).

The objective of this study was to describe the most common and rarer types of MODY in cases with genetically confirmed diagnoses in a single center cohort, and to evaluate the clinical diagnostic characteristics, genetic analysis results, follow-up, and treatment features of these patients.

Methods

Cases

The study was conducted retrospectively, analyzing the epidemiological, auxological, laboratory, genetic, and treatment data of 44 patients diagnosed with MODY and followed in two pediatric endocrinology clinics in Malatya between January 2013 and December 2020. The epidemiological data included age, gender, parental consanguinity, and family history of diabetes. Auxological data consisted of height (cm), weight (kg), and body mass index (BMI; kg/m²). Laboratory data included glucose, insulin, C-peptide, hemoglobin A1c (HbA1c), lipid profile (total cholesterol, total triglycerides, high-density lipoprotein, low-density lipoprotein, urine ketones, and diabetes autoantibodies. Genetic analysis results and treatment regimens were also retrospectively evaluated from patient follow-up records.

The auxological evaluations of the patients, conducted using standard measurement tools with a precision of 0.1 kg for weight and 0.1 cm for height, were performed using the auxology section of the ÇEDD-NET calculation system. This system was developed by the Turkish Society of Pediatric Endocrinology and Diabetes for use by pediatricians and pediatric endocrinology physicians (5).

For a classic MODY diagnosis, the following criteria were used: dominant inheritance with at least two (preferably three) consecutively affected generations (though *de novo* mutations have been reported); onset of diabetes typically before the age of 25 to 30 years; evidence of significant but impaired residual insulin secretion, reflected in C-peptide levels, regardless of whether the patient is treated with insulin; negative tests for antibodies associated with type 1 diabetes mellitus (T1DM), although again, very rare exceptions have been reported; and stable, mild, non-progressive hyperglycemia in asymptomatic individuals, suggesting *GCK*-MODY (3,4).

Genetic Analysis

At least three generation pedigrees of the cases were formed. Genomic DNA was extracted from peripheral blood with QiAamp DNA Blood Mini Kit (cat. no. 51106, Qiagen, Hilden, Germany). Next generation sequencing was performed by capture of the all exons and 10 bp exon-intron junctions of the 14 target MODY genes (*ABCC8, APPL1, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, PAX4,* and *PDX1*). Prior to library preparation, each sample was diluted to a fixed concentration of 20 ng using nuclease-free water, as required by the kit. Sequencing libraries were prepared according to the manufacturer's instructions. After library enrichment and quality control, the samples were sequenced using the Illumina MiSeq platform (Illumina, San Diego, CA, USA) with 100 bp paired-end reads at an average sequencing depth of 100x. Demultiplexed FASTQ files were processed individually using Qiagen Bioinformatics solutions. The sequencing reads were aligned to the human genome reference, GRCh37 (Genome Reference Consortium human build 37). Annotation of detected variants was performed using InterVar, Franklin, VarSome, ClinVar, OMIM, and Pubmed. Variants with a frequency higher than 0.5% were filtered out. dbNSFP (contains SIFT, PolyPhen-2, LRT, and Mutation Taster) was used to predict the pathogenicity of variants. Rare variants were classified according to the American College of Medical Genetics and Genomics/the Association for Molecular Pathology variant interpretation framework (6). Segregation analyzes were performed on family members who consented to be included in this study.

Statistical Analysis

Statistical calculations were performed using the Statistical Package for Social Sciences, version 29.0 (IBM Corp., Armonk, NY, USA). Quantitative variables that followed a normal distribution are expressed as mean and standard deviation (SD), while those that did not confirm to normal distribution were reported as median (minimum-maximum). Qualitative variables were expressed as frequency and percentage.

Results

In the 44 patients included in the study, the male-to-female ratio was 1.58:1. The mean birth weight (n = 40) was 3078 ± 514.8 g. Ten patients (22.7%) had additional (extrapancreatic) diseases/findings. The extrapancreatic findings included attention deficit hyperactivity disorder (two patients), epilepsy (two patients), intellectual disability (one patient), hepatosteatosis (one patient), asthma (one patient), ectopic kidney (one patient), increased echogenicity of the renal parenchyma (one patient), hypertension (one patient), juvenile idiopathic arthritis (one patient), primary ovarian insufficiency (one patient), arhythmia (one patient), and precocious puberty (one patient). Imaging studies (abdominal ultrasound/magnetic resonance imaging) were performed in 31 (70.4%) patients, with no pathological findings reported. The other clinical and laboratory findings of the patients are presented in Table 1.

As a presenting complaint, incidental hyperglycemia was significantly more common in patients diagnosed with *GCK*-MODY, while polyuria and polydipsia were more prevalent in other MODY types ($p < 0.05$). Diabetic ketoacidosis was detected only in MODY cases other than *GCK*-MODY ($p < 0.05$). The HbA1c levels were significantly higher in non-*GCK*-MODY cases ($p < 0.05$). While the majority of *GCK*-MODY cases were treated with lifestyle changes alone, the use of pharmacotherapy in addition to lifestyle modifications was significantly more common in non-*GCK*-MODY ($p < 0.05$). The simultaneous positivity of two tested diabetes autoantibodies was observed only in non-*GCK*-MODY. The genes and mutations identified in the cases are shown in Table 2.

Characteristics of *GCK*-MODY Patients

In the 25 patients diagnosed with *GCK*-MODY, the male-to-female ratio was 1.5. Four patients (16%) had additional (extrapancreatic) diseases/findings. The additional findings included one patient with a combination of intellectual disability, primary ovarian insufficiency, and arrhythmia, while the other three patients presented with precocious puberty, epilepsy, and juvenile idiopathic arthritis, respectively. Ketonemia was detected in one patient diagnosed with *GCK*-MODY (Patient 3 in Table 3). This patient's fasting blood glucose at presentation was 950 mg/dL, with a C-peptide level of 0.43 ng/mL, fasting insulin of 1.99 µU/mL, and an HbA1c of 11.6%. Anti-GAD positivity was also identified in this patient, who was subsequently treated with insulin. During follow-up, the HbA1c value decreased to 7.4%. All patients were provided with an appropriate dietary program. Only two patients received metformin therapy. These patients had a BMI greater than the 95th percentile, with one showing impaired glucose tolerance (IGT) on oral glucose tolerance test (OGTT), while the other had a postprandial glucose level in the diabetic range. Except for the patient who started insulin therapy, all other patients maintained an HbA1c level below 7% during their initial assessment and follow-up. The mutations detected in the *GCK* gene and the clinical characteristics of the patients are shown in Table 3.

Characteristics of non-*GCK*-MODY Cases

Among the four patients diagnosed with *HNF1A*-MODY, three were related. The average age at presentation was 11.2 years. All patients had BMI SD score values within the normal range. Three diabetes autoantibodies [anti-glutamic acid decarboxylase (anti-GAD), islet cell antibodies (ICA), insulin autoantibodies (IAA)] were assessed in these cases. Only one patient (Patient 2 in Table 4) tested positive for two diabetes autoantibodies (anti-GAD and ICA). This patient presented with fasting hyperglycemia and an HbA1c level in the prediabetic range, with a normal OGTT result. The patient treated with diet alone maintained an HbA1c level within the normal range. One of the other three patients (Patient 4 in Table 4) had normal fasting glucose and HbA1c levels at presentation and continued to remain within the normal range with dietary management. The remaining two patients had fasting glucose and HbA1c values at diabetic levels. Ketonemia was detected in one of these patients at

Table 1. Clinical and laboratory features of patients diagnosed with MODY

	MODYs (n = 44)	*GCK*-MODY (n = 25)	Non-*GCK* MODYs (n = 19)
Male/female	1.58	1.5	1.71
Age at diagnosis, (years)	10 (± 4.19)	9.85 (± 4.19)	10.36 (± 4.29)
Positive family history, n (%)	42 (95.45)	24 (96)	18 (94.73)
Consanguineous marriage, n (%)	10 (22.72)	7 (28)	3 (15.78)
Mean BMI-SDS	-0.45 (± 1.45)	-0.28 (± 1.26)	-0.68 (± 1.66)
BMI > 95th p, n (%)	4 (9.1)	3 (12)	1 (5.26)
BMI < 5th p, n (%)	10 (22.72)	3 (12)	7 (36.84)
Incidental hyperglycemia, n (%)	23 (52.27)	19 (76)	4 (21)
Polyuria-polydipsia, n (%)	14 (31.81)	2 (8)	12 (63.15)
DKA, n (%)	4 (9.1)	0	4 (21.05)
Diabetic ketonemia, n (%)	3 (6.8)	1 (4)	2 (10.52)
Triglyceride, (mg/dL)	91.05 (± 46.79)	85.33 (± 45.63)	99 (± 48.80)
Total cholesterol, (mg/dL)	158.88 (± 34.54)	152.90 (± 26.22)	167.26 (± 43.25)
HDL-cholesterol, (mg/dL)	49.41 (± 15.11)	49.77 (± 13.13)	48.92 (± 18)
LDL-cholesterol, (mg/dL)	90.83 (± 28.51)	86 (± 23.29)	97.58 (± 34.25)
HbA1c, (%)	7.78 (± 2.98)	6.49 (± 1.17)	9.48 (± 3.75)
Fasting insulin (IU/L)	6.68 (± 7.06)	6.24 (± 4.57)	7.29 (± 9.64)
C-peptide, (ng/mL)	1.24 (± 0.95)	1.21 (± 0.62)	1.27 (± 1.29)
Fasting glucose, (mg/dL)	210.5 (± 202.7)	159.3 (± 169.4)	277.9 (± 226.9)
Anti-GAD (+), n (%)	7 (15.9)	3 (12)	4 (21)
Anti-ICA (+), n (%)	7 (15.9)	2 (8)	5 (26.3)
Anti-IAA (+), n (%)	2 (4.5)	1 (4)	1 (5.2)
Anti-GAD + anti-ICA (+), n (%)	4 (9)	0	4 (21)
Anti-ICA + anti-IAA (+), n (%)	1 (2.3)	0	1 (5.2)
Only diet and lifestyle changes, n (%)	26 (59)	22 (88)	4 (21)
Diet and lifestyle changes + oral antidiabetic drugs and/or insulin, n (%)	18 (41)	3 (12)	15 (78.9)
Diet and lifestyle changes and oral antidiabetic drugs and insulin n (%)	6 (13.6)	0	6 (31.5)

BMI: body mass index, DKA: diabetic ketoasidosis, HDL: high density lipoprotein, LDL: low density lipoprotein GAD: glutamic acid decarboxylase, ICA: islet cell antibodies, IAA: insulin autoantibodies, MODY: maturity-onset diabetes of the young, GCK: glucokinase, SDS: standard deviation score, HbA1c: hemoglobin A1c

Table 2. Genes with variation detected in MODY cases and patient numbers

Gene	*GCK*	*HNF1a*	*CEL*	*BLK*	*ABCC8*	*KLF11*	*INS*	*KCNJ11*	*APPL1*
n = 44	25	4	4	2	4	2	1	1	1
%	56.8	9.1	9.1	4.5	9.1	4.5	2.3	2.3	2.3

GCK: glucokinase, *HNF1a*: hepatocyte nuclear factor-1-alpha, *CEL*: carboxyl ester lipase, *BLK*: B lymphocyte kinase, *ABCC8*: ATP-binding cassette subfamily C member 8, *KLF11*: Kruppel-like factor 11, *INS*: insulin, *KCNJ11*: potassium channel, inwardly rectifying, subfamily J member 11, *APPL1*: adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1

Table 3. Clinical and laboratory features of *GCK*-MODY cases

Patient	Gender	Age (Year)	Presentation	Positive family history	BMI (%)	Transcript number/variant	Protein	Zygosity	ACMG classification	Diabetes autoantibody positivity	Treatment
1	M	7.2	Polyuria- polydipsia	3 generations	25-50	NM_00134800.1: c.904 G > C	p.Val302Met	Heterozygous	Likely pathogenic	GAD	Only diet
2	M	13.2	Incidental hyperglycemia	No[ǂ]	5-15	NM_00134800.1: c.565 A > G	p.I189V	Homozygous	Likely pathogenic	-	Only diet
3	M	5.4	Polyuria- polydipsia	3 generations	25-50	NM_000162.5: c.565A > G	p.I189V	Heterozygous	Likely pathogenic	GAD*	Insulin
4	F	16.6	Incidental hyperglycemia	3 generations	> 95	NM_00134800.1: c.667 G > A	p.Gly223Ser	Heterozygous	Pathogenic	GAD	Metformin
5	M	11.6	Incidental hyperglycemia	3 generations	25-50	NM_00134800.1: c.239 G > C	p.Gly80Ala	Heterozygous	Pathogenic	-	Only diet
6	M	7.5	Incidental hyperglycemia	3 generations	25-50	NM_00134800.1: c.1195 G > T	p.Glu399*	Heterozygous	Pathogenic	-	Only diet
7	M	2.6	Incidental hyperglycemia	F + 3 generations	85-95	NM_000162.5: c.736G > C	p.G246R	Heterozygous	Pathogenic	-	Only diet
8	F	16.8	Incidental hyperglycemia	M + F + 3 generations[ǂ]	< 5	NM_00134800.1: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Only diet
9	F	2.4	Incidental hyperglycemia	F + B/S + 3 generations	5-15	NM_00134800.1: c.565 A > G	p.I189V	Homozygous	Likely pathogenic	-	Only diet
10	F	14	Absence of menarche	3 generations[ǂ]	50-75	NM_033507.3: c.-16_-2delTTAGCCCCTCGGAGA	-	Heterozygous	VUS	-	Only diet
11	F	10.5	Incidental hyperglycemia	M(GDM) + 3 generations	> 95	NM_00134800.1: c.667 G > A	p.Gly223Ser	Heterozygous	Pathogenic	-	Only diet
12	F	11.1	Incidental hyperglycemia	F + 3 generations	15-25	NM_00134800.1: c.704 T > C	p.Met235Thr	Heterozygous	Pathogenic	-	Only diet
13	M	2.9	Family history of diabetes	F + B/S + 3 generations	15-25	NM_000162.5: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Only diet
14	M	8.1	Family history of diabetes	F + B/S + 3 generations	5-15	NM_00134800.1: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
15	M	13.1	Family history of diabetes	M(GDM) + B/S[ǂ]	50-75	NM_00134800.1: c.565 A > G,	p.I189V	Homozygous	Likely pathogenic	-	Only diet
16	F	11	Incidental hyperglycemia	M + 3 generations	5-15	NM_00134800.1: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
17	M	6.4	Incidental hyperglycemia	F + B/S + 3 generations	75-85	NM_000162.5: c.1178T > C	p.M393T	Heterozygous	Pathogenic	IAA	Only diet
18	M	12.1	Incidental hyperglycemia	M + 3 generations	5-15	NM_00134800.1: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Only diet
19	M	12.8	Incidental hyperglycemia	M(GDM) + F + 3 generations	< 5	NM_00134800.1: c.1009 C > T	p.Gln337X	Heterozygous	Pathogenic	-	Only diet
20	F	11.5	Incidental hyperglycemia	No	50-75	NM_000162.5: c.565A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
21	M	16.4	Incidental hyperglycemia	M + 3 generation[ǂ]	15-25	NM_00134800.1: c.667 G > A	p.Gly223Ser	Heterozygous	Pathogenic	ICA	Only diet
22	M	7.5	Incidental hyperglycemia	M(GDM) + B/S[ǂ]	75-85	NM_00134800.1: c.565 A > G	p.I189V	Homozygous	Likely pathogenic	-	Only diet
23	F	6.6	Incidental hyperglycemia	M + 3 generations	15-25	NM_00134800.1: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	-	Only diet
24	M	8.6	Incidental hyperglycemia	M + 3 generations[ǂ]	> 95	NM_000162.5: c.1178T > C	p.M393T	Heterozygous	Pathogenic	-	Metformin
25	F	9.5	Incidental hyperglycemia	3 generations	< 5	NM_000162.5: c.565 A > G	p.I189V	Heterozygous	Likely pathogenic	ICA	Only diet

Patients 15 and 22 are cousins; Patients 13 and 17 are brothers; Patients 9 and 14 are brothers.

ǂ: consanguineous marriage; *: presented with ketonemia.

M: mother, F: father, B/S: brother/sister, GDM: gestational diabetes mellitus, VUS: variant of uncertain significance, GAD: glutamic acid decarboxylase, ICA: islet cell antibodies, IAA: insulin autoantibodies, BMI: body mass index, ACMG: American College of Medical Genetics and Genomics, GCK: glucokinase

Table 4. Clinical and laboratory features of non-*GCK*-MODY cases

Patient	Gender	Age (Year)	Presentation	Positive family history	BMI (%)	Gene	Transcript number/ variation	Protein	Zigosity	ACMG classification	Diabetes autoantibody positivity	Treatment
1	F	13.1	Incidental hyperglycemia	M + F + B/S + 3 generations	50-75	*HNF1A*	NM_000545.8: c.526 + 1 G > C	-	Heterozygous	Pathogenic	-	Metformin
2	M	9.1	Incidental hyperglycemia	M + F + B/S + 3 generations‡	75-85	*HNF1A*	NM_000545.8: c.526 + 1 G > C	-	Heterozygous	Pathogenic	GAD, ICA	Only diet
3	F	14.8	Polyuria-polydipsia	M + F + B/S + 3 generations‡	50-75	*HNF1A*	NM_000545.8: c.526 + 1 G > C	-	Heterozygous	Pathogenic	-	Met + Ins[2]
4	M	7.8	Polyuria-polydipsia	M + 4th degree relative	15-25	*HNF1A*	NM_000545.8: c.716 C > T	p.Ala239Val	Heterozygous	Likely pathogenic	-	Only diet
5	M	15.7	Polyuria-polydipsia	B/S + 2nd degree relative	< 5	*CEL*	NM_001807.6: c.1454T > C	p.Ile485Thr	Heterozygous	VUS	GAD, ICA	Met + Ins
6	F	12	Not gaining weight	3 generations	< 5	*CEL*	NM_001807.6: c.460G > A	p.G154 > R	Heterozygous	VUS	-	Only diet
7	M	11	Polyuria-polydipsia	3rd degree relative	15-25	*CEL*	NM_001807.5: c.1454T > C	p.Ile485Thr	Heterozygous	VUS	-	Met + Ins
8	F	1	Polyuria-polydipsia	3 generations	5-15	*CEL*	NM_001807.5: c.1974delC	p.V659fs*45	Heterozygous	Likely pathogenic	GAD, ICA	Insulin[1]
9	M	3.3	Low C-peptide	3 generations	15-25	*BLK*	NM_001715.3: c.391C > T	p.R131W	Heterozygous	VUS	-	Only diet
10	M	13.7	Overweight	3 generations	85-95	*BLK*	NM_001715.3: c.773-5C > G	-	Heterozygous	VUS	-	Metformin
11	M	5	Polyuria-polydipsia	M	< 5	*ABCC8*	NM_000352.6: c.1261G > A	p.V421I	Heterozygous	Likely pathogenic	-	Insulin[1]
12	F	10.8	Polyuria- polydipsia	No	< 5	*ABCC8*	NM_000352.6: c.1261G > A	p.V421I	Heterozygous	Likely pathogenic	-	Insulin[2]
13	M	15.2	Incidental hyperglycemia	3 generations	> 95	*ABCC8*	NM_000352.6: c.1252T > C	p.C418R	Heterozygous	VUS	-	Met + ins
14	M	12.4	Polyuria-polydipsia	M + 2nd degree relative‡	85-95	*ABCC8*	NM_000352.6: c.2617C > T	p.L873F	Heterozygous	VUS	-	Metformin
15	M	6.7	Polyuria-polydipsia	2nd degree relative	85-95	*KLF11*	NM_003597.5: c.308C > T	p.T103I	Heterozygous	VUS	-	Insulin[1]
16	F	9.7	Polyuria-polydipsia	3 generations	< 5	*KLF11*	NM_003597.5: c.145G > A	p.Glu49Lys	Heterozygous	VUS	IAA, ICA	Met + Ins
17	F	6.7	Polyuria-polydipsia	3 generations	5-15	*KCNJ11*	NM_000525.4: c.595_596delATinsGG	p.M199G	Heterozygous	Likely pathogenic	GAD, ICA	Insulin
18	M	13	Polyuria-polydipsia	3 generations + 2nd degree relative	< 5	*INS*	NM_000207.3: c.71C > T	p.A24V	Heterozygous	Pathogenic	-	Insulin[1]
19	M	15.3	Incidental hyperglycemia	3 generations	< 5	*APPL1*	NM_012096.3: c.2018C > G	p.S673C	Heterozygous	VUS	-	Met + Ins

‡: consanguineous marriage; [1]: presented with ketoacidosis; [2]: presented with ketonemia.

M: mother, F: father, B/S: brother/sister, GDM: gestational diabetes mellitus, VUS: variant of uncertain significance, GAD: glutamic acid decarboxylase, ICA: islet cell antibodies, IAA: insulin autoantibodies.

HNF1A: hepatocyte nuclear factor-1-alpha, CEL: carboxyl ester lipase, BLK: B lymphocyte kinase, ABCC8: ATP-binding cassette subfamily C member 8, KLF11: Kruppel-like factor 11, INS: insulin, KCNJ11: potassium channel, inwardly rectifying, subfamily J member 11, adaptor protein, phosphotyrosine interaction, pH domain, and leucine zipper containing 1

presentation, who was treated with insulin, while the other patient was managed with oral antidiabetic agents.

Among the four patients diagnosed with *CEL*-MODY, one presented with an increase in renal parenchyma echogenicity as an additional condition, while another had an ectopic kidney. Renal function was found to be normal in both cases. One patient (Patient 7 in Table 4) presented with intermittent abdominal pain related to meals, and the fecal elastase value was measured at 117 µg/mL (normal: > 200 µg/mL; mild exocrine pancreatic insufficiency: 100-200 µg/mL; exocrine pancreatic insufficiency: < 100 µg/mL), indicating mild exocrine pancreatic insufficiency, and was referred to the pediatric gastroenterology department for dietary management. Although the c.1454T > C variant detected in this patient was classified as benign by some databases, the detection of exocrine pancreatic insufficiency seen in *CEL*-MODY led us to classify this variant as a variant of uncertain clinical significance (VUS). Fecal elastase levels could not be evaluated in other cases. At presentation, all patients had normal c-peptide levels. Two patients (Patients 5 and 8 in Table 4) tested positive for two diabetes autoantibodies (anti-GAD and ICA) simultaneously. One (Patient 6 in Table 4) presented with failure to gain weight and was normoglycemic but had an HbA1c value in the prediabetic range. This patient's OGTT was normal, and during follow-up, the HbA1c value normalized with dietary management. The other three patients had HbA1c values at diabetic levels and were treated with insulin.

Of the two patients diagnosed with *BLK*-MODY, one was overweight while the other had a normal BMI. At presentation, the overweight patient had fasting hyperglycemia and prediabetic HbA1c, while the other patient (Patient 9 in Table 4) had fasting hyperglycemia, low C-peptide and normal HbA1c. The overweight patient was treated with metformin, while the other patient was monitored with diet modification alone. During follow-up, their HbA1c levels remained below 6%.

Of the four patients diagnosed with *ABCC8*-MODY, one was obese, one was overweight, and two were malnourished, based on their BMIs. Three patients had diabetic fasting glucose and HbA1c levels, while one patient had only prediabetic HbA1c levels (6.2%) (Patient 14 in Table 4). One of the patients with malnutrition had ketoacidosis (Patient 11 in Table 4), and the other had ketosis (Patient 12 in Table 4). All three diabetes autoantibodies (anti-GAD, ICA, IAA) were found to be negative. Two patients with ketosis and ketoacidosis were treated with insulin, while the patient with obesity was treated with insulin after a short period of metformin use. The patient who was overweight and had a prediabetic HbA1c level was followed up with oral antidiabetics. The patient, whose treatment compliance was poor, had a final HbA1c level of 7%.

Two patients were diagnosed with *KLF11*-MODY; one was overweight and had diabetic levels of glucose and HbA1c and was treated with insulin. The other patient had malnutrition, presenting with fasting hyperglycemia and a diabetic HbA1c level of 6.8%. This patient showed IGT on the OGTT, and two diabetes autoantibodies (ICA and IAA) were positive. Initially treated with metformin, this patient's treatment was later supplemented with insulin. This patient also had attention deficit hyperactivity disorder as an additional condition.

The genetic and clinical characteristics of non-*GCK*-MODY cases are summarized in Table 4.

Discussion

Approximately 80% of MODY cases are misdiagnosed as type 1 or type 2 diabetes, which complicates prevalence and incidence estimates (7). MODY is considered the most common form of monogenic diabetes, accounting for approximately 1-6.3% of diabetes cases reported in the literature (2,8,9,10,11,12).

Genes causing MODY affect insulin secretion by disrupting insulin release, glucose metabolism in pancreatic beta cells, or activating ATP-dependent potassium channels. Patients typically have heterozygous mutations. Penetrance and expressivity can vary significantly among family members (13). In our cohort, most patients (90.9%) had heterozygous mutations, while only four patients had homozygous mutations. Among the homozygous patients, three had a history of parental consanguinity.

GCK-MODY is one of the most common types of MODY among European Caucasians (14). In Türkiye, various studies conducted in children have also identified *GCK*-MODY as the most frequently detected type of MODY (15,16,17,18,19). One study found that approximately one in four children diagnosed with MODY had *GCK*-MODY (19). In the present study, *GCK*-MODY was the most prevalent type, accounting for well over half (56.8%) of cases. The mutations most frequently identified in the *GCK* gene, p.M393T and p.I189V, which are classified as potentially pathogenic, have also been detected in two previous studies conducted in Türkiye (20,21).

Although *GCK*-MODY is known as an untreated form of MODY characterized by mild, non-progressive fasting hyperglycemia in childhood, and no complications (1), one of our *GCK*-MODY patients (Patient 3 in Table 3) received insulin therapy. As in this patient, a case report from Italy

presented cases of siblings who were both positivefor diabetes autoantibody (1 or 2 of them) and had the same *GCK* gene variant, and treated with intermittent insulin and continuous insulin (22). Although a single diabetes autoantibody positivity has a poor predictive value for the diagnosis of T1DM, considering that only three diabetes autoantibodies were measured in our patient. It is possible that this patient may have been positive for other diabetes antibodies that were not evaluated. Thus, we believe this case may be a rare case of *GCK*-MODY and type 1 diabetes coexisting.

Mutations in the *HNF1A* and *GCK* genes have been identified as the most common causes of MODY in many studies conducted in Europe, North America, and some Asian countries (2,23). In the present study, *HNF1A*-MODY was detected in less than 10% of the cohort, which was the same rate as for *CEL*-MODY and *ABCC8*-MODY (all n = 4). This finding is unusual and suggests that the observed rate of *CEL*-MODY in our cohort was higher than that reported in many studies conducted both in our country and in the world. However, as the cohort size was modest, then this may simply be an effect of the smaller numbers.

Diabetes autoantibody positivity (anti-GAD, anti-ICA, anti-IAA) was detected in a quarter of the patients. This rate is higher than the diabetes autoantibody positivity rate of 11.2% found in the largest multicenter study conducted in our country, which presented 224 patients with MODY (19). Among these, five patients exhibited positivity for two autoantibodies simultaneously. Anti-ICA positivity was present in a total of 7/11 cases, and in addition to this antibody, four patients were positive for anti-GAD (*CEL, HNF1A, KCNJ11, KLF11*), while one case demonstrated positivity for anti-IAA (*KLF11*). Variants detected with diabetes autoantibody positivity are shown in Table 3 and Table 4 and five of these variants are classified as likely pathogenic, four as pathogenic, and two as VUS.

Twenty-six (59%) of the cases were treated with lifestyle changes and diet alone and of these 22 were *GCK*-MODY, which was also 88% of all *GCK*-MODY cases. Eighteen (41%) of the cases were treated with oral antidiabetics and/or insulin. Six cases used both oral antidiabetics and insulin during the treatment process. These cases are shown in Table 4.

Study Limitations

The retrospective nature of the study, the small number of cases, the detection of many variants of unknown clinical significance in genes associated with MODY, especially in the *CEL* gene, as a result of genetic analysis, and the inability to perform segregation analysis and functional studies in these cases are the factors limiting this study. Another limitation of the study was that the diabetes autoantibodies (anti-GAD, ICA, IAA) tests were performed in external laboratories, so detailed information about the method used (ELISA or immunofluorescence) was not available. Furthermore, since quantitative values were not available for all cases, these data are presented only as 'positive' and 'negative'.

Conclusion

To date, many different genes have been identified as causes of MODY, each with distinct clinical characteristics and most requiring different treatments. Therefore, the impact of accurate biomolecular genetic diagnosis is significant for many patients, as it can lead to the cessation of inappropriate treatment, for example, insulin injections, after several years of therapy. However, many patients remain undiagnosed or experience long delays between the initial diabetes diagnosis and the correct genetic diagnosis. Thus, in cases where the type of diabetes is uncertain, biomarkers used in differential diagnosis (clinical, metabolic, immune, genetic) should be carefully evaluated and, if necessary, reassessed during follow-up.

In addition, clarifying the genetic etiology is important for identifying individuals at risk. Genetic studies, functional studies, and larger case series are needed to identify new MODY-related loci and to elucidate genotype-phenotype correlations. In coming years, the introduction of gene-targeted therapies will likely contribute to the management of these cases.

Ethics

Ethics Committee Approval: The study received approval from the Clinicial Research Ethics Committee of Malatya Training and Research Hospital (approval number: 23536505-604.02, date: 17.08.2020).

Informed Consent: Segregation analyzes were performed on family members who consented to be included in this study.

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Footnotes

Authorship Contributions

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