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Research Article

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

Kayaş L et al. MODY in Childhood

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What is already known about this topic.?
MODY is a monogenic form of diabetes mellitus. To date, 14 different genes associated with MODY have been reported (*HNF4α, GCK, HNF1α, PDX1, HNF1β, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11,* and *APPL1*). The diagnosis of MODY includes dominant inheritance with at least two (preferably three) consecutive affected generations, onset of diabetes typically before the age of 25–30 years, evidence of significant but impaired residual insulin secretion reflected in c-peptide levels, negative tests for autoantibodies associated with T1DM in most cases (very rare exceptions have been reported), and stable, mild, nonprogressive hyperglycemia suggestive of GCK-MODY in asymptomatic individuals.

What this study adds to the literature?
As in various studies conducted in children in our country, the most frequently detected MODY type in our study was GCK-MODY. Although MODY is generally known as an autoantibody-negative type of diabetes (especially islet antibody), autoantibody positivity was detected in one-quarter of the cases in our study and more than half of these were anti-islet 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 β-cell development or function. Our study aimed to define the most common and rare types of MODY in our cases with genetically confirmed MODY diagnosis, to evaluate clinical and laboratory features and treatment regimens.
Methods: The epidemiological, auxological, laboratory data, genetic analysis results and treatment regimens of 44 patients diagnosed with MODY were retrospectively evaluated.
Results: Of the cases included, 27 (61.4%) were male and the mean 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%) *GCK*, 4 (9.1%) *HNF1A*, 4 (9.1%) *CEL*, 2 (4.5%) *BLK*, 4 (9.1%) *ABCC8*, 2 (4.5%) *KLF11*, 1 (2.3%) *INS*, 1 (2.3%) *KCNJ11*, 1 (2.3%) *APPL1.* At presentation, 23 (52.3%) of the cases had incidental hyperglycemia, 14 (31.8%) had polyuria and polydipsia. Diabetic ketoacidosis was detected in 4 (9.1%) and ketonemia in 3 (6.8%). At least one of the diabetes autoantibodies (anti-GAD, anti-ICA, anti-IAA) was detected in 11 (25%) cases, of which 7 were islet antibodies, and 5 cases (11%) had two autoantibodies positive at the same time. 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%) of them received both oral antidiabetic agents and insulin.
Conclusion: The most common type of MODY in our study 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 our study.
Keywords: MODY, diabetes autoantibodies, childhood.

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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 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 as follows: 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*), 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*), 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 characterised by the absence of ketosis and the absence of insulin dependence, with a diagnosis of diabetes occurring before the age of 25. Additionally, 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, and to evaluate the clinical diagnostic characteristics, genetic analysis results, follow-up, and treatment features of these patients.

Materials and Methods

Cases

The study was conducted retrospectively, analyzing the epidemiological, auxological, laboratory, genetic, and treatment data of 44 patients diagnosed with MODY and followed by 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 involved glucose, insulin, c-peptide, HbA1c, cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), 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 pediatric 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 can occur); onset of diabetes typically before the age of 25 to 30; 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 (T1DM), with very rare exceptions 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). New generation sequencing was performed by capture of the all exones with 10bp exon-intron junctions of 14 target MODY genes (*ABCC8, APPL1, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, PAX4, PDX1*). Prior to library preparation, the appropriate dilution was made for each sample. 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 100bp 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 were 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, Mutation Taster) was used to predict the pathogenicity about the deleteriousness of variants. Rare variants were classified according to the American College of Medical Genetics and Genomics (ACMG)/the Association for Molecular Pathology (AMP) 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 trial version of SPSS software (www.ibm.com/tr-tr/analytics/spss-trials-SPSS V27) (7). Quantitative variables that followed a normal distribution were expressed as mean and standard deviation, while those that did not conform 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. 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, epilepsy, intellectual disability, hepatosteatosis, asthma, ectopic kidney, increased echogenicity of the renal parenchyma, hypertension, juvenile idiopathic arthritis, primary ovarian insufficiency, arrhythmia, and precocious puberty. Imaging studies (abdominal ultrasound/MRI) were performed in 31 patients (70.4%), 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 cases ($p < 0.05$). Diabetic ketoacidosis (DKA) was detected only in MODY cases other than GCK-MODY ($p < 0.05$). The HbA1c levels were significantly higher in MODY cases other than GCK-MODY ($p < 0.05$). While GCK-MODY cases were treated solely with lifestyle changes, the use of pharmacotherapy in addition to lifestyle modifications was significantly higher in cases other than GCK-MODY ($p < 0.05$). The simultaneous positivity of two tested diabetes autoantibodies was observed only in cases other than GCK-MODY.

The genes and mutations identified in the cases are shown in Table 2.

Characteristics of GCK-MODY Cases

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 (Case 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 level 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 the 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 SDS values within the normal range. Three diabetes autoantibodies (Anti-GAD, ICA, IAA) were assessed in these cases. Only one patient (Case 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 monitored with diet alone maintained an HbA1c level within the normal range. One of the other three patients (Case 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 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 (Case 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 carried by this case was classified as benign in 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. Fecal elastase levels could not be evaluated in other cases. At presentation, all patients had normal c-peptide levels. Two patients (Cases 5 and 8 in Table 4) tested positive for two diabetes

autoantibodies (Anti-GAD and ICA) simultaneously. A patient (Case 6 in Table 4) presenting with failure to gain weight 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.
Among the two patients diagnosed with BLK-MODY, one was overweight while the other had normal BMI. At presentation, the overweight patient had fasting hyperglycemia and prediabetic HbA1c, while the other patient (Case 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 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 according to BMI. Three patients had diabetic fasting glucose and HbA1c levels, while one patient had only prediabetic HbA1c levels (6.2%) (Case 14 in Table 4). One of the patients with malnutrition had ketoacidosis (Case 11 in Table 4), and the other had ketosis (Case 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 low, had a final HbA1c level of 7%.
Among the two patients diagnosed with KLF11-MODY, the overweight patient 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 impaired glucose tolerance on the OGTT, and two diabetes autoantibodies (ICA and IAA) tested 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 (8). MODY is considered the most common form of monogenic diabetes, accounting for approximately 1-6.3% of diabetes cases reported in the literature (2,9-13).
Genes of MODY, affect insulin secretion by disrupting insulin release, glucose metabolism in beta cells, or activating adenosine triphosphate (ATP)-dependent potassium channels. Patients typically have heterozygous mutations. Penetrance and expressivity can vary significantly among family members (14). In our cohort, 40 patients (90.9%) had heterozygous mutations, while 4 patients (9.1%) had homozygous mutations. Among the homozygous patients, three had a history of consanguinity.
GCK-MODY is one of the most common types of MODY among European Caucasians (15). In Turkey, various studies conducted in children have also identified GCK-MODY as the most frequently detected type of MODY (16-19). One study found that approximately one in four children diagnosed with MODY had GCK-MODY (20). In our study, GCK-MODY was the most prevalent type, accounting for 56.8% (n = 25) 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 studies conducted in Turkey (20,21).
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 (2,22). In our study, HNF1A-MODY was detected at a rate of 9.1% (n = 4), which is the same as the rate for CEL-MODY and ABCC8-MODY.
Diabetes autoantibody positivity (Anti-GAD, Anti-ICA, Anti-IAA) was detected in 11 of the cases (25%). This rate is higher than what has been reported so far in the literature. Among these, 5 cases (11.4%) exhibited positivity for two autoantibodies simultaneously. Anti-ICA positivity was present in a total of 7 cases, and in addition to this antibody, four cases showed positivity 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. Five of these variants are classified as likely pathogenic, four as pathogenic, and two as variants of uncertain significance (VUS).
Twenty-six (59%) of the cases were treated with lifestyle changes and diet alone. Twenty-two of these cases were GCK-MODY, which was 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.

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 insulin injections years later. However, many patients remain undiagnosed or experience long delays between the initial diabetes diagnosis and the correct genetic diagnosis (23). 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 (24). Additionally, 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 the coming years, the introduction of gene-targeted therapies will contribute to the management of these cases.

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Conflict Of Interest

No conflict to interest.

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Table 1: Clinical and laboratory features of Mody cases

	MODYs (n=44)	GCK-MODY (n=25)	Non-GCK MODYs (n=19)
Male/Female	1.58	1.5	1.71
Age of 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)
BMI-SDS mean	-0.45 (±1.45)	-0.28 (±1.26)	-0.68 (±1.66)
BMI>95p n (%)	4 (9.1)	3 (12)	1 (5.26)
BMI<5 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 İnsülin (ıu/l)	6.68 (±7.06)	6.24 (±4.57)	7.29 (±9.64)
C-Peptid (ng/ml)	1.24 (±0.95)	1.21 (±0.62)	1.27 (±1.29)
Fasting Glikoz (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 insülin 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: Insülin autoantibodies,

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

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

Patient	**Gender**	**Age (Year)**	**Presentation**	**Positive family history**	**BMI (%)**	**Transcript number/Variation**	**Protein**	**Zigosity**	**ACMG Classification**	**Diabetes Autoantibody Positivity**
1	E	7.2	Polyuria- polydipsia	3. generation	25-50	NM_00134800.1: c.904 G>C	p.Val302Met	Heterozygous	Likely pathogenic	GAD
2	E	13.2	Incidental hyperglycemia	Not ǂ	5-15	NM_00134800.1: c.565 A>G	p.I189V	**Homozygous**	Likely pathogenic	-
3	E	5.4	Polyuria- polydipsia	3. generation	25-50	NM_000162.5: c.565A>G	p.I189V	Heterozygous	Likely pathogenic	GAD *
4	K	16.6	Incidental hyperglycemia	3. generation	>95	NM_00134800.1: c.667 G>A	p.Gly223Ser	Heterozygous	Pathogenic	GAD
5	E	11.6	Incidental hyperglycemia	3. generation	25-50	NM_00134800.1: c.239 G>C	p.Gly80Ala	Heterozygous	Pathogenic	-
6	E	7.5	Incidental hyperglycemia	3. generation	25-50	NM_00134800.1: c.1195 G>T	p.Glu399*	Heterozygous	Pathogenic	-
7	E	2.6	Incidental hyperglycemia	F+ 3. generation	85-95	NM_000162.5: c.736G>C	p.G246R	Heterozygous	Pathogenic	-
8	K	16.8	Incidental hyperglycemia	M+F+3.generation ǂ	<5	NM_00134800.1: c.1178T>C	p.M393T	Heterozygous	Pathogenic	-
9	K	2.4	Incidental hyperglycemia	F+B/S+3. generation	5-15	NM_00134800.1: c.565 A>G	p.I189V	**Homozygous**	Likely pathogenic	-
10	K	14	Absence of menarche	3. generation ǂ	50-75	NM_033507.3: c.-16_-2delTTAGCCCCTCGGAGA	-	Heterozygous	VUS	-
11	K	10.5	Incidental hyperglycemia	M(GDM)+3. generation	>95	NM_00134800.1: c.667 G>A	p.Gly223Ser	Heterozygous	Pathogenic	-
12	K	11.1	Incidental hyperglycemia	F+3. generation	15-25	NM_00134800.1: c.704 T>C	p.Met235Thr	Heterozygous	Pathogenic	-

13	E	2.9	Family history of diabetes	F+B/S+3. generation	15-25	NM_000162.5: c.1178T>C	p.M393T	Heterozygous	Pathogenic	-
14	E	8.1	Family history of diabetes	F+B/S+3. generation	5-15	NM_00134800.1: c.565 A>G	p.I189V	Heterozygous	Likely pathogenic	-
15	E	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	-
16	K	11	Incidental hyperglycemia	M+ 3. generation	5-15	NM_00134800.1: c.565 A>G	p.I189V	Heterozygous	Likely pathogenic	-
17	E	6.4	Incidental hyperglycemia	F+B/S+3. generation	75-85	NM_000162.5: c.1178T>C	p.M393T	Heterozygous	Pathogenic	IAA
18	E	12.1	Incidental hyperglycemia	M+ 3. generation	5-15	NM_00134800.1: c.1178T>C	p.M393T	Heterozygous	Pathogenic	-
19	E	12.8	Incidental hyperglycemia	M(GDM)+F+ 3. generation	<5	NM_00134800.1: c.1009 C>T	p.Gln337X	Heterozygous	Pathogenic	-
20	K	11.5	Incidental hyperglycemia	Not	50-75	NM_000162.5: c.565A>G	p.I189V	Heterozygous	Likely pathogenic	-
21	E	16.4	Incidental hyperglycemia	M+3. generation ǂ	15-25	NM_00134800.1: c.667 G>A	p.Gly223Ser	Heterozygous	Pathogenic	ICA
22	E	7.5	Incidental hyperglycemia	M(GDM)+ B/S ǂ	75-85	NM_00134800.1: c.565 A>G	p.I189V	**Homozygous**	Likely pathogenic	-
23	K	6.6	Incidental hyperglycemia	M+ 3. generation	15-25	NM_00134800.1: c.565 A>G	p.I189V	Heterozygous	Likely pathogenic	-
24	E	8.6	Incidental hyperglycemia	M+3. generation ǂ	>95	NM_000162.5: c.1178T>C	p.M393T	Heterozygous	Pathogenic	-
25	K	9.5	Incidental hyperglycemia	3. generation	<5	NM_000162.5: c.565 A>G	p.I189V	Heterozygous	Likely pathogenic	ICA

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: insülin autoantibodies, ǂ: Consanguineous marriage, *: Presenting with ketonemia

15 and 22, numbered cases cousin, 13 and 17 numbered cases brother, 9 and 14 numbered cases brother, 3 numbered case treated with insülin

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	K	13.1	Incidental hyperglycemia	M+F+B/S+.3. generation	50-75	*HNF1A*	NM_000545.8: c.526+1 G>C	-	Heterozygous	Pathogenic	-	Metformin
2	E	9.1	Incidental hyperglycemia	M+F+B/S+.3. generation ǂ	75-85	*HNF1A*	NM_000545.8: c.526+1 G>C	-	Heterozygous	Pathogenic	GAD, ICA	Only diet
3	K	14.8	Polyuria-polydipsia	M+F+B/S+.3. generation ǂ	50-75	*HNF1A*	NM_000545.8: c.526+1 G>C	-	Heterozygous	Pathogenic	-	Met+İns ²
4	E	7.8	Polyuria-polydipsia	M+4. degree relative	15-25	*HNF1A*	NM_000545.8: c.716 C>T	p.Ala239Val	Heterozygous	Likely pathogenic	-	Only diet
5	E	15.7	Polyuria-polydipsia	B/S+2. degree relative	<5	*CEL*	NM_001807.6: c.1454T>C	p.Ile485Thr	Heterozygous	VUS	GAD, ICA	Met+İns
6	K	12	Not gaining weight	3. generation	<5	*CEL*	NM_001807.6: c.460G>A	p.G154>R	Heterozygous	VUS	-	Only diet
7	E	11	Polyuria-polydipsia	3. degree relative	15-25	*CEL*	NM_001807.5: c.1454T>C	p.Ile485Thr	Heterozygous	VUS	-	Met+İns
8	K	1	Polyuria-polydipsia	3. generation	5-15	*CEL*	NM_001807.5: c.1974delC	p.V659fs*45	Heterozygous	Likely pathogenic	GAD, ICA	İnsülin ¹
9	E	3.3	C peptid düşüklüğü	3. generation	15-25	*BLK*	NM_001715.3: c.391C>T	p.R131W	Heterozygous	VUS	-	Only diet
10	E	13.7	Overweight	3. generation	85-95	*BLK*	NM_001715.3: c.773-5C>G	-	Heterozygous	VUS	-	Metformin
11	E	5	Polyuria-polydipsia	M	<5	*ABCC8*	NM_000352.6: c.1261G>A	p.V421I	Heterozygous	Likely pathogenic	-	İnsülin ¹
12	K	10.8	Polyuria-polydipsia	Not	<5	*ABCC8*	NM_000352.6: c.1261G>A	p.V421I	Heterozygous	Likely pathogenic	-	İnsülin ²
13	E	15.2	Incidental hyperglycemia	3. generation	>95	*ABCC8*	NM_000352.6: c.1252T>C	p.C418R	Heterozygous	VUS	-	Met+ins
14	E	12.4	Polyuria-polydipsia	M+2. degree relative ǂ	85-95	ABCC8	NM_000352.6: c.2617C>T	p.L873F	Heterozygous	VUS	-	Metformin
15	E	6.7	Polyuria-polydipsia	2. degree relative	85-95	*KLF11*	NM_003597.5: c.308C>T	p.T103I	Heterozygous	VUS	-	İnsülin ¹
16	K	9.7	Polyuria-polydipsia	3. generation	<5	*KLF11*	NM_003597.5: c.145G>A	p.Glu49Lys	Heterozygous	VUS	IAA, ICA	Met+İns
17	K	6.7	Polyuria-polydipsia	3. generation	5-15	*KCNJ11*	NM_000525.4: c.595_596delATinsGG	p.M199G	Heterozygous	Likely pathogenic	GAD, ICA	İnsülin
18	E	13	Polyuria-polydipsia	3. generation+2. degree relative	<5	*INS*	NM_000207.3: c.71C>T	p.A24V	Heterozygous	Pathogenic	-	İnsülin ¹
19	E	15.3	Incidental hyperglycemia	3. generation	<5	*APPL1*	NM_012096.3: c.2018C>G	p.S673C	Heterozygous	VUS	-	Met+İns

ǂ: Consanguineous marriage, M: Mother, F: Father, B/S: Brother/Sister, Met: Metformin, İns: İnsülin, VUS: Variant of uncertain significance, GAD: Glutamic acid decarboxylase, ICA: Islet cell antibodies, IAA: Insülin autoantibodies, ¹: Presenting with ketoacidosis ²: Presenting with ketonemia