Original Article

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Maturity-onset Diabetes of the Young (MODY): How Much Can We Detect?

Gençlerde Başlayan Erişkin Tipi Diyabet (MODY): Ne Kadarını Yakalayabiliyoruz?

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ABSTRACT

Objective: This study aims to assess the characteristics of patients who underwent genetic analysis with suspicion of maturity-onset diabetes of the young (MODY).

Methods: Forty patients who met the criteria of measurable serum fasting C-peptide levels, positive family history, and autoantibody negativity and were diagnosed with diabetes at a young age were analyzed for demographic, clinical, laboratory and molecular test results. A comprehensive MODY panel examining a total of 21 genes [*hepatocyte nuclear factor 4 alpha (HNF4A), glucokinase (GCK), HNF 1 alpha (HNF1A), pancreatic and duodenal homeobox 1, HNF 1 beta (HNF1B), neurogenic differentiation 1, kruppel-like factor 11, carboxyl ester lipase, paired box gene 4, insulin, B-lymphocyte kinase, adenosine triphosphate binding cassette sub-family C member 8, potassium inwardly rectifying channel subfamily J member 11, AKT2, GLI-similar 3, glutamate dehydrogenase 1, hydroxyacyl-CoA dehydrogenase, insulin receptor, solute carrier family 2 member 2, wolfram syndrome 1, zinc finger protein 57*] in 30 patients (75%) with next-generation sequencing method and variants detected in 10 patients (25%) using a short panel including *GCK, HNF1A, HNF1B and HNF4A* genes were analyzed using different databases (online mendelian inheritance in man, database of single nucleotide polymorphisms, genome aggregation database, human gene mutation database).

Results: Overall, 11 variants in 7 different genes were detected in 10 patients (25%). Sixty per cent (n=6) of the mutation-positive patients were treated with insulin. Serum fasting C-peptide levels (1.18 vs 1.26 ng/mL, p=0.891) and age at diabetes diagnosis (26.5

ÖZ

Amaç: Bu çalışmanın amacı gençlerde başlayan erişkin tipi diyabet (MODY) şüphesi ile genetik analiz yapılan hastaların özelliklerini değerlendirmektir.

Yöntemler: Ölçülebilir serum açlık C-peptid düzeyleri, pozitif aile öyküsü, otoantikor negatifliği gibi kriterlere uyan ve genç yaşta diyabet tanısı alan 40 hastanın demografik, klinik, laboratuvar ve moleküler test sonuçları incelendi. Tamamı yeni nesil dizileme yöntemi ile 30 hastada (%75), 21 genin [*hepatosit nükleer faktör 4 alfa (HNF4A), glukokinaz (GCK), HNF 1 alfa (HNF1A), pankreatik ve duodenal homeobox 1, HNF 1 beta (HNF1B), nörojenik farklılaşma 1, kruppel benzeri faktör 11, karboksil ester lipaz, paired box proteini 4, insülin, B lenfoid tirozin kinaz, adenozin trifosfat bağlı kompaktörü subfamilisi C üyesi 8, potasyum inwardly rectifying kanal subfamiliyası J üyesi 11, AKT2, GLIS ailesi çinko parmak proteini 3, glutamat dehidrogenaz 1, hidroksi asil-koa dehidrogenaz , insülin reseptörü, sitozol membran taşıyıcı 2 , wolfram sendrom 1 proteini, çinko parmağı proteini 57*] incelendiği kapsamlı MODY paneli ve 10 hastada (%25) *GCK, HNF1A, HNF1B ve HNF4A* genlerini içeren kısa panel kullanılarak saptanan varyantlar, farklı veri tabanları (insanlarda çevrim içi mendel kalıtımı veritabanı, tek nükleotid polimorfizmi veritabanı, genom toplulaştırma veritabanı, insan gen mutasyonları veritabanı) kullanılarak analiz edildi.

Bulgular: Tüm hastalar içinde 10 hastada (%25) toplam 7 ayrı gende, 11 varyant tespit edildi. Mutasyon pozitif hastaların %60'ı (n=6) insülin kullanmaktaydı. Mutasyon pozitif ve negatif gruplar arasındaki serum açlık C-peptid düzeyleri (1,18'e 1,26 ng/mL,

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ABSTRACT

vs 29.0 years, p=0.860) were not different between the mutation-positive and mutation-negative groups.

Conclusion: Despite the improved diagnosis, MODY diagnosis is still missed and a significant number of patients are unnecessarily treated with insulin. In particular, individuals diagnosed with diabetes at a young age, with negative autoantibodies and measurable serum C-peptide levels, should be evaluated for MODY.

Keywords: MODY, next-generation sequence analysis, *GCK, HNF1A, HNF4A*

ÖZ

p=0,891) ve diyabet tanısı aldıkları yaşlar (26,5'e 29,0 yıl, p=0,860) arasında fark yoktu.

Sonuç: Gelişen tanı imkânlarına rağmen MODY hastaları hala gözden kaçmakta ve önemli bir kısmı gereksiz yere insülin ile tedavi edilmektedir. Özellikle genç yaşta diyabet tanısı alan, otoantikorları negatif, ölçülebilir serum C-peptid düzeyleri olan hastalar, MODY açısından gözden geçirilmelidir.

Anahtar Kelimeler: MODY, yeni nesil dizi analizi, *GCK, HNF1A, HNF4A*

Introduction

Diabetes is a chronic, progressive metabolic disease caused by interacting genetic and environmental factors. It is characterized by hyperglycemia and associated with impaired lipid, protein and carbohydrate metabolism. So far, more than 300 polymorphisms have been identified in type 2 diabetes that may play a role in its pathophysiology (1-3). Highly penetrant monogenic forms of diabetes, such as maturity-onset diabetes of the young (MODY), provide evidence that rare genetic variants can cause diabetes. Developments in the field of genetics will provide a better understanding of the role of genetics in diabetes in the future (2).

MODY describes a genetic disorder with early onset of diabetes (usually before age 25), a positive family history, autosomal dominant inheritance, and a lack of ketosis without significant insulin deficiency (1,4-6).

Currently, there are 14 genes definitively associated with MODY types; *hepatocyte nuclear factor 4 alpha (HNF4A), glucokinase (GCK), HNF 1 alpha (HNF1A), pancreatic and duodenal homeobox 1 (PDX1), HNF 1 beta (HNF1B), neurogenic differentiation 1 (NEUROD1), kruppel-like factor 11 (KLF11), carboxyl ester lipase (CEL), paired box gene 4 (PAX4), insulin (INS), B lymphocyte kinase (BLK), adenosine triphosphate binding cassette sub-family C member 8 (ABCC8), potassium inwardly rectifying channel subfamily J member 11 (KCNJ11), and adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1* (7-11). The most common mutations in MODY are in *HNF1A, GCK, HNF4A, HNF1B and INS* genes. Almost all cases in the literature that can be definitively linked to MODY have a mutation in one of these 5 genes (10,12,13). The most common MODY gene mutations are *GCK* and *HNF1A* mutations. *GCK* mutations seem to be at the forefront in some countries, while *HNF1A* mutations are reported more frequently in others (14). The most common mutation, *GCK*, has been found in a relatively small number of studies in our country (15-17).

The only accepted method in diagnosing MODY is detecting the genetic mutation using a molecular test. Classically, clinical MODY is characterized by onset before the age of 25 years, the presence of diabetes in two consecutive generations, the absence of beta-cell autoantibodies and the preservation of endogenous insulin secretion (fasting serum C-peptide levels ≥0.6 ng/mL) (4-6). However, clinical criteria alone are insufficient for diagnosing MODY (13). Studies have shown that up to 95% of MODY patients are misdiagnosed and receive unnecessary insulin treatment (18,19). Misclassification will likely cause over-intervention or unnecessary increases in health care and treatment costs (20).

There has been evidence of the efficacy of sulfonylurea treatment in MODY patients since the 1990s, and there has been no significant change in treatment to date (21,22). It is well known that the tendency towards more expensive and complex treatments for diabetes is increasing worldwide. The use of sulfonylureas has halved in the last decade, and this situation leads to patients with undiagnosed monogenic diabetes receiving more costly and unindicated treatments unnecessarily every day (23-25).

Although it is a relatively expensive test, genetic analysis in correctly selected patients is a cost-effective method of avoiding unnecessary treatment and screening for comorbidities, but its effectiveness in reducing longevity and comorbidities has not been demonstrated (26).

Our study aimed to investigate the characteristics of patients who underwent genetic analysis with suspicion of MODY and to investigate the genotype-phenotype relationship of the detected variants.

Methods

Study Design

The medical records and genetic results of patients who underwent genetic analysis for suspected MODY at the Internal Medicine and Endocrinology Outpatient Departments of the İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital were retrospectively analyzed.

Age, age at onset of diabetes, sex, body mass index (BMI), waist circumference (cm), systolic and diastolic blood pressure (mmHg), family history of diabetes, history of diabetic ketoacidosis (DKA), history of previous diseases and operations, and previous treatments were noted. Biochemical analyses of the patients were as follows: glucose (mg/dL), glycated hemoglobin A1c (HbA1c, %), islet cell antibody (ICA, positive/negative), glutamic acid decarboxylase antibody (GADA, IU/mL), insulin autoantibody (IAA, IU/mL), serum C-peptide (ng/

mL), low-density lipoprotein cholesterol (LDL-C, mg/dL), high DL-C (HDL-C, mg/dL), triglycerides (TG, mg/dL), alanine aminotransferase (ALT, IU/L), aspartate aminotransferase (IU/L), spot urine protein-to-creatinine ratio, and C-reactive protein (CRP, mg/dL) values were recorded in the database. For all patients diagnosed with diabetes under 35 (as it cannot be calculated above this age), the probability of MODY was calculated using the model at https://www.diabetesgenes.org/ and added to the patient data.

Ethics committee approval was obtained from the Ethics Committee of İstanbul Medeniyet University (no: 2020/0619, date: 26.10.2020). This study was conducted according to the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients with suspected MODY who underwent genetic analysis were included. Since the study was conducted in an adult outpatient clinic, patients under 18 years of age were not included.

Genetic Analysis

The main MODY panel (*GCK, HNF1A, HNF1B and HNF4A*) and the comprehensive MODY panel (*HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11, AKT2, GLI-similar 3, glutamate dehydrogenase 1, hydroxyacyl-CoA dehydrogenase, INS receptor, solute carrier family 2 member 2, wolfram syndrome 1 (WFS1), zinc finger protein 57*) were used for genetic analysis.

Deoxyribonucleic acid was routinely isolated from the patients' peripheral blood for genetic analysis. The genes in the test panel were amplified by exon-specific (amplicon) multiplex polymerase chain reaction and analyzed on the IlluminaMiseq next-generation sequencing platform using the capture-based method. The Mutation Taster model, available at http://www.mutationtaster.org/, was used as an in silico bioinformatics program using sequence conservation and structure-based algorithms to calculate the pathogenicity probabilities of new variants detected during the study (27).

The resulting data were analyzed using Burrows-Wheeler aligner (0.7.12-r1034), PicardTools 2.17.3, Genome Analysis Tool Kit 3.7 and ANNOVAR. The analysis was reported using the human genome hg19 and several databases [OMIM, single nucleotide polymorphism database (dbSNP), ClinVar, dbNSFP, Genome Aggregation Database (gnomAD), 1000 Genomes, Exome Sequencing Project, Exome Aggregation Consortium, Ensembl, HapMap CEU and Human Gene Mutation Database (HGMD)]. Variants were also reported according to the American College of Medical Genetics and Genomics (ACMG) classification to assess the level of pathogenicity (28). We re-used these databases and updated the analyses of the variants before the publication date of the study.

Statistical Analysis

Analyses were performed using the IBM SPSS version 22 program (IBM Corp., Armonk, NY, USA). Descriptive statistical methods used to analyze the data were number, percentage, minimum and maximum, median, mean and standard deviation. The conformity of the quantitative data to the normal distribution was tested using the Shapiro-Wilk test, the Box-Plot test, histogram plots, the number of cases in the study, and the mean and standard deviation values (29). T-test (two-tailed Student's t-test) for parametric variables and Mann-Whitney U test for non-parametric variables were used for statistical comparisons between mutation-positive and mutation-negative groups. A p-value of 0.05 was accepted as the threshold for statistical significance. In addition, the analyses were performed again, excluding the two siblings who were found to be involved in the analysis and similar results were found (data not shown).

Results

A total of 40 patients were included in the analysis. Demographic and clinical characteristics, including sex distribution, current age, and age at diagnosis, are summarized in Table 1.

A positive family history of diabetes was present in 90% (n=36) of the patients. There was no family history of diabetes in 10% of the patients (n=4). A history of DKA was present in 5% (n=2) of the patients.

Chronic diseases other than diabetes were present in 60% (n=24) of the patients; dyslipidemia (n=10), hypertension (n=9), hypothyroidism (n=4), allergic rhinitis or rheumatoid arthritis (n=2 each), and other conditions (n=12). Treatment for comorbidities other than diabetes was recorded in 42.5% (n=17) of the patients; 9 patients had a history of statin use, 9 had a history of angiotensin-converting enzyme inhibitor or

Table 1. Clinical, physical and laboratory characteristics of patients suspected of having MODY

Characteristics	Mean or % ± SD (Min.-Max.)
Female	48%
Age, year	40.1 (19-62)
Age at diagnosis of diabetes, year	28.4 (13-48)
HbA1c	8.5±2.3%
FPG, mg/dL	179.6±89.7
C-peptide, ng/mL	1.24±0.76
Insulin therapy	50%
Family history of diabetes	90%
Statin use	23%
BMI, kg/m^2	25.3 (18.4-40.3)
Waist circumference, cm	
Male	87.6 (78-101)
Female	84.0 (68-120)
Systolic blood pressure, mmHg	120.3±10.8
Diastolic blood pressure, mmHg	77.6±7.9

MODY: Maturity-onset diabetes of the young, SD: Standard deviation, Min.: Minimum, Max: Maximum, HbA1c: Glycated hemoglobin, FPG: Fasting plasma glucose, BMI: Body mass index

angiotensin receptor blocker use, 2 had a history of thiazide diuretic use, 1 had a history of calcium channel blocker use, and 1 had a history of beta-blocker use. In the analysis of complications of diabetes, 20% of patients (n=8) had a history of complications; 3 patients had retinopathy or neuropathy, and 1 patient had nephropathy or peripheral arterial disease.

The mean MODY probability percentage of the patients sent for gene analysis was 30.8±27.1%. The percentage of four patients could not be calculated because the calculator could not calculate those diagnosed above the age of 35 years.

Physical measurements such as BMI, waist circumference, and blood pressure are summarized in Table 1.

Laboratory characteristics including HbA1c, fasting plasma glucose, and serum C-peptide levels are presented in Table 2.

When the cases were analyzed regarding the 3 diabetes autoantibody tests (ICA, GADA, IAA) performed in our hospital, it was observed that 60% (n=24) were negative for all three autoantibodies. One autoantibody was positive in 10% (n=4), and two autoantibodies were positive in 2.5% (n=1) of cases; none of the patients were positive for all three autoantibodies.

Table 2. Laboratory characteristics of patients suspected of having MODY

Characteristics	Mean or % ± SD (Min.-Max.)
Diabetes-specific autoantibodies	
ICA	3%
GADA	8%
IAA	5%
CRP, mg/dL	2.11±0.93
Spot urine protein/creatinine	0.18±0.16
ALT, U/L	21.8±19.6
LDL, mg/dL	116.5±30.4
HDL, mg/dL	53.4±14.1
TG, mg/dL	169.0±139.8

Spot urine protein (mg/dL), creatinine (mg/dL)
MODY: Maturity-onset diabetes of the young, ICA: Islet cell cytoplasmic autoantibodies, GADA: Glutamic acid decarboxylase autoantibody, IAA: Insulin autoantibody, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, TG: Triglyceride, ALT: Alanine transaminase, CRP: C-reactive protein

Table 3. Genetic test result distribution in patients with suspected MODY

Result	**Mutation-negative**	**n=30**	**25%**
	Mutation-positive	**n=10**	**75%**
ACMG classification of positive variants	Pathogenic	2	
	Potentially pathogenic	6	
	VUS	2	

VUS: A variant of uncertain clinical significance, ACMG: American College of Medical Genetics

Among the cases sent for molecular analysis, one patient (2.5%) had ICA positive, and three patients (7.5%) had GADA positive. IAA was positive in two patients (5%) who were known to receive insulin treatment. The autoantibody titer was in the borderline positive range in cases with positive autoantibodies.

Genetic variants were detected in 25% (n=10) of patients. Details of the identified variants and their ACMG classifications are presented in Table 3.

When the patients were compared between those mutation-positive and mutation-negative, it was found that the waist circumference of mutation-positive female patients was significantly thinner (87.7±13.0 vs 73.0±8.0 cm, p=0.011). No differences were observed regarding gender, age, age at diagnosis of diabetes, HbA1c, average plasma glucose, serum C-peptide, history of DKA, insulin treatment, how long insulin has been in use since diagnosis, family history of diabetes, history of non-diabetes chronic diseases, in diabetes complications, MODY probability percentage, BMI, a waist circumference of male patients, systolic and diastolic blood pressure, autoantibodies, CRP, spot urine protein/creatinine ratio, ALT, LDL-C, HDL-C, TG, statin use. A detailed comparison of mutation-positive and mutation-negative patients is provided in Supplementary Table.

In 10 cases (25%), 11 rare heterozygote sequence variants were identified in 7 genes. Two variants were observed in the *GCK* gene, two in the *HNF1A* gene, two in the *HNF4A* gene, one in the *BLK* gene, two in the *ABCC8* gene, one in the *INSR* gene and two in the *WFS1* gene. These consisted of 9 missenses (82%), 1 nonsense (9%) and 1 deletion-frameshift (9%) variant. Eight of them (*GCK* c.943C>T, *HNF1A* c.864delG, *HNF1A* c.1513C>A, *BLK* c.T1013C, *ABCC8* c.2539G>A, *ABCC8* c.1252T>C, *WFS1* c.1672C>T, *WFS1* c.2020G>A) were registered in databases. According to the ACMG classification of the 3 new variants, *GCK* c.91A>T was considered pathogenic, *HNF4A* c.1004G>A was considered potentially pathogenic, and *INSR* c.913G>A was considered variants of uncertain significance (VUS). The mutations identified by the bioinformatics program were predicted to be "damaging" and likely to affect protein function. There were 12 variants detected in the study, but two separate cases carried the same variant in the *WFS1* gene (Tables 4 and 5).

Discussion

Our study revealed the presence of a genetic factor in 10 (25%) of 40 patients who underwent genetic analysis with clinical suspicion of MODY. Prospective and retrospective studies in Türkiye have shown mutation detection rates ranging from 17 to 65%, while international studies have shown mutation detection rates ranging from 7 to 97% (14-17). The observed differences between studies are most likely explained by the different selection criteria used for genetic testing. The mutation detection rates in studies with patient selection by physician decision, such as ours, are similar to or lower than those in our study (13,30). This may be attributed to the fact that genetic testing is often performed without adherence to the standardized patient selection criteria

recommended by MODY guidelines. Additionally, there appears to be a lack of awareness regarding MODY and other forms of monogenic diabetes among physicians working in adult outpatient clinics. It was also thought that some genes related to MODY may not yet have been discovered, or limitations related to testing panels may also contribute to this. The next-generation sequencing method used in the genetic analysis of patients can detect single nucleotide changes with 99% accuracy, as well as small deletions and insertions (up to 10-15 bases). However, detecting large deletions, duplications, insertions, changes in long homopolymer sequences and copy number variants in genes is insufficient. This suggests that some of the remaining mutation-negative patients may have mutations in MODY genes that have not yet been identified.

Although next-generation sequencing has revolutionized clinical diagnostic testing, kits examining deep intronic sequence and promoter variations have not yet become widespread due to cost.

As kits examining these regions become more common in the future, the proportion of variants that can be detected in similar

Table 4. Genetic characteristics of patients with variants and their equivalents in databases

No	Gene (locus)	Associated phenotype (#OMIM no)	DNA exchange AA exchange	Mutation type Zygosity	HGMD	dbSNP	ACMG classification*
2	*GCK* (NM_000162)	MODY, type 2 (# 125851)	c.91A>T p.Lys31*	Nonsense Heterozygote	No information available	No information available	PVS1, PM1, PM2, PP3 "pathogenic"
14	*GCK* (NM_000162.5)	MODY, type 2 (# 125851)	c.943C>T p.L315F	Missense Heterozygote	CM064013 "MODY 2"	Rs1583594350 "VUS"	PM1, PM2, PP2, BP3, PP5, PM5 "potentially pathogenic"
17	*HNF1A* (NM_000545)	MODY, type 3 (#600496)	c.864delG p.P291Qfs*51	Del-FS Heterozygote	CM082856 "MODY 3"	Rs762703502 "pathogenic"	PVS1, PP5, PM2 "pathogenic"
40	HNF1A (NM_000545.6)	MODY, Type. 3 (#600496)	c.1513C>A p.H505N	Missense Heterozygote	CM082823 "MODY 3"	No information available	PM2, PP2, PP3, PP5 "potentially pathogenic"
20	*HNF4A* (NM_000457.4) *BLK* (NM_001715)	MODY, type 1 (# 125850) MODY, type 11 (#613375)	c.1004G>A p.G335E c.T1013C p.I338T	Missense Heterozygote Missense Heterozygote	No information available CM1416414 "Autism spectrum disorder"	No information available No information available	PM1, PM2, PP2, PP3 "potentially pathogenic" PM2, PP3 "VUS"
11	*ABCC8* (NM_000352.4)	DM, non-insulin-dependant (#125853)	c.l252T>C p.C418R	Missense Heterozygote	CM994414 "Hypoglycemia persistent hyperinsulinemic"	RS67254669 "VUS"	PM2, PP2 "VUS"
31	*ABCC8* (NM_000352.6)	DM, non-insulin-dependant (#125853)	Cc.2539G>A p.A847T	Missense Heterozygote	CM148394 "Hyperinsulinemic hypoglycemia"	RS561593131 "VUS"	PS1, PM1, PM2, PP2, BP4 "potentially pathogenic"
39	*INSR* (NM_000208.4)	DM, insulin-resistant (#610549)	c.913G>A P.V305I	Missense Heterozygote	No information available	No information available	PM1, PM2 "VUS"
37	*WFS1* (NM_006005.3)	DM, non-insulin-dependant (#125853)	c.1672C>T p.R558C	Missense Heterozygote	CM015264 "Wolfram's syndrome"	Rs199946797 "pathogenic"	PM2, PM5, PP5, PP3 "potentially pathogenic"
21	*WFS1* (NM_006005.3)	DM, non-insulin-dependant (#125853)	c.2020G>A p.G674R	Missense Heterozygote	CM011519 "Wolfram's syndrome"	RS200672755 "pathogenic"	PM2, PP3, PP5 "potentially pathogenic"
			c.1672C>T p.R558C	Missense Heterozygote	CM015264 "Wolfram's syndrome"	Rs199946797 "pathogenic"	PM2, PM5, PP2, PP3 "potentially pathogenic"

*In the recommendations of the ACMG standards and guidelines, each pathogenic criterion is classified as very strong (PVS1), strong (PS1-4), moderate (PM1-6) or supportive (PP1-5), and each benign criterion as benign (BP1-5).
OMIM no: Online mendelian inheritance in man phenotype number, DNA: Deoxyribonucleic acid, AA: Amino acid, HGMD: Human gene mutation database (access code given if the information is available in the database), dbSNP: Single nucleotide polymorphism database (access code given if the information is available in the database), ACMG: American College of Medical Genetics, Del-FS: Deletion/frameshift,VUS: A variant of uncertain clinical significance,

studies will increase.

Of the variants identified as "disease cause for MODY" by the HGMD database, 3 were detected in patients 14, 17 and 40 (*GCK* c.943C>T; p.L315F, *HNF1A* c.864delG; p.P291Qfs*51 and *HNF1A* c.1513C>A; p.H505N, respectively). The variants of the other 7 patients were registered as probable for MODY or of uncertain clinical significance.

A review of clinicians' decisions to perform genetic testing revealed that 90% of patients had a family history of diabetes, and the mean age at diagnosis was 28.4±7.6 years. Since diabetes is a common disease, the presence of diabetes in a few family members does not necessarily indicate hereditary diabetes. However family history is an accurate first approach to selecting patients with MODY (31). Mutation-positive patients in our study were diagnosed with diabetes approximately 2.5 years (26.5±8.8 vs. 29.0±7.2 years) earlier. This supports a genetic basis in these patients.

Most variants in this study were missense mutations (82%), which can affect protein stability or cause loss of critical catalytic domains. These results were similar to studies in other European populations where missense mutations predominate (32-34). In addition, nonsense and a frameshift mutation were identified that can cause premature termination of protein synthesis or the formation of nonsense ribonucleic acid (35).

Two patients (5%) who underwent molecular testing with suspicion of MODY but no mutation was detected had a history of hospitalization with suspected DKA. A history of DKA in patients with MODY is usually not an expected finding because endogenous insulin production may continue for years, but history alone does not exclude MODY (36). The reason for this is

Table 5: Clinical and laboratory characteristics of patients with variants

No	G	Age	AD	BMI	WC	A1c	C-p	Chronic D	Complication	MO%	Affected relative	Treat	Gene	Variant	Mut
2	F	32	18	18.4	68	7.2	0.88	-	-	75.5	Mother, father, uncle, brother	OAD+ Insulin	*GCK*	c.91A>T p.Lys31*	Nons
14	F	28	22	21.9	68	6.8	1.12	-	-	75.5	Father, sibling	OAD	*GCK*	C.943C>T P.L315F	Miss
17	F	41	35	19.7	70	8.2	1.33	-	-	24.4	Mother, father, brother, sister	OAD	*HNF1A*	c.864delG p.P291Qfs*51	Del/ Fr.
40	F	28	16	25.8	0	6.8	0.62	-	-	75.5	Mother, father, brother, sister	Insulin	*HNF1A*	C.1513C>A P.H505N	Miss
20	F	58	26	20.1	72	7.6	0.63	Dyslipidemia HT Hypothyroid	NP	62.4	Father	OAD+ Insulin	*HNF4A* *BLK*	c.l004G>A P.G335E C.T1013C P.I338T	Miss
11	M	19	13	33.1	101	13.2	3.11	Autism epilepsy	-	0.7	Grandfather, mother, father, uncle	OAD+ insulin	*ABCC8*	c.1252T>C P.C418R	Miss
31	M	38	35	27.0	94	7.4	1.99	-	-	15.1	Grandmother, father	LSM	*ABCC8*	C.2539G>A P.A847T	Miss
39	F	62	32	26.7	87	8.3	0.27	Dyslipidemia	PAD	4.6	Father, uncle, daughter	OAD+ Insulin	*INSR*	c.913G>A P.V305I	Miss
37	M	46	38	19.3	78	10.2	1.10	A. Rhinitis		Ø	Sibling	LSM	*WFS1*	c.1672C>T P.R558C	Miss
21	M	56	30	24.2	85	8.2	0.72	HT	RP	15.1	Sibling	Insulin	*WFS1*	c.2020G>A P.G674R C1672C>T P.R558C	Miss

G: Gender, F: Female, M: Male; AD: Age at diagnosis of diabetes (years); BMI: Body mass index (kg/m^2); WC: Waist circumference (cm), A1c: Glycated hemoglobin (%), C-p: Serum fasting C-peptide (ng/mL), Chronic D: Chronic disease, MO%: MODY probability percentage, Treat: Treatment for diabetes, Mut: Mutation type; ACMG: American College of Medical Genetics classification, HT: Hypertension, A. rhinitis: Allergic rhinitis, NP: Neuropathy, PAD: Peripheral arterial disease, RP: Retinopathy, OAD: Oral antidiabetic drug, LSM: Lifestyle modification, Miss: Missense, Del: Deletion, Fr: Frameshift, Ø: Unknown or incalculable

that there have been reports in the literature of cases of *HNF1A*-MODY, the majority of which had DKA with insulin deficiency in the later stages of the disease (37).

The first case (no: 22) was a 30-year-old diabetic patient with 25 years of diabetes mellitus and a fasting serum C-peptide level of 0.42 ng/mL, who was prescribed insulin 10 years after diagnosis and had DKA in the 21st year after diagnosis and the second case (no: 28) was a 27-year-old diabetic patient with 29 years of diabetes mellitus and a fasting serum C-peptide level of 0.48 ng/mL, who was prescribed insulin during hospitalization with DKA 10 years after diagnosis. No variant was detected in the genetic analysis of both cases.

In case 2, the *GCK* variant was a novel mutation causing premature stop codon formation. It is known that the HbA1c level of *GCK*-MODY patients rarely exceeds 7.5%, and there are even publications in the literature that set a limit of 7.3% for requesting genetic testing (9,38). This case was a 32-year-old, 14-year-old diabetic patient with a serum fasting C-peptide level of 0.88 ng/mL and an HbA1c level of 7.2% under metformin, sitagliptin and insulin glargine treatment. This new mutation (c.91A>T; p.Lys31*) was not a primary missense mutation but a nonsense mutation causing a termination codon resulting in reduced functional glucokinase protein (39). This supports the possibility of high pathogenicity. Several studies have shown that insulin secretion in patients with nonsense and frameshift mutations in the MODY genes is impaired more severely or at an earlier stage than in those with missense mutations. This is more likely to lead to the use of insulin (40-42). This is explained by the fact that a MODY patient with *GCK* mutation was diagnosed under insulin therapy, for whom treatment is not usually recommended (43).

Case 14, who had a different variant in the *GCK* gene, was a patient being followed up with metformin and dapagliflozin treatment and underwent genetic analysis on suspicion of MODY. A c.943C>T; p.L315F missense variant was found and classified as a "disease-causing mutation" in the HGMD database and VUS in the dbSNP database.

Case 17 was a 35-year-old patient diagnosed with *HNF1A*-MODY by detecting c.864delG; p.P291Qfs*51 deletion, frameshift variant when the HbA1c level was 8.2, who had been on diabetes treatment for 6 years, and who showed dramatic improvement in glycemic control after switching to gliclazide treatment. Unlike missense mutations, this mutation, which is classified as pathogenic according to ACMG criteria and the dbSNP database as in patient 2, causes a loss-of-function mutation (PVS1) of the gene product due to deletion of a guanine nucleotide, resulting in a frameshift in protein translation and a change in protein length. The presence of individuals diagnosed with diabetes in the family also supports the presence of this variant with a high risk of phenotyping.

The c.1513C>A; p.H505N variant in the *HNF1A* gene detected in patient 40 was "potentially pathogenic" according to ACMG criteria and had a frequency of 0.0000797 (gnomAD). This mutation, whose functional effect is mostly considered "damaging" by in silico prediction tools, was registered as a "disease-causing mutation" for MODY 3 in the HGMD database. The fasting serum C-peptide level was 0.62 ng/mL, and the postprandial C-peptide level was 1.76 ng/mL, while the pre-treatment HbA1c level was 12.6%, and it was 6.8% under basal insulin glargine treatment only.

Interestingly, case 20 had an HNF4A variant (c.1004G>A; p.G335E) and a BLK variant (c.T1013C; p.I338T) that were not previously included in databases and could not be classified as pathogenic. Although the patient had two variants associated with MODY and predicted to be "damaging" by in silico prediction tools, and had diabetes for 32 years, the possible reason for the delayed diagnosis of MODY was the increased prevalence of genetic testing in recent years and the presence of comorbidities such as dyslipidemia and hypertension, which are common with type 2 diabetes mellitus (T2DM). This pattern was compatible with MODY type 1 and type 11 disease, which may present with signs of insulin resistance such as dyslipidemia, weight gain and high insulin requirement. This may also be an additive effect of mutations. Previously, cases with two different MODY mutations and developing different or more severe presentations than expected have been reported in the literature (44-46). All this evidence suggests the importance of screening for other genes, especially for patients with an unexplained or severe clinical pattern.

Case 11 with a 3-gen family history of diabetes, epilepsy and autism since age 2, diagnosed with diabetes at age 13, heterozygous c.1252T>C (p.C418R) missense mutation in *ABCC8* gene, eating disorder secondary to Autism, had no evidence of insulin resistance other than obesity. The *ABCC8* gene mutation associated with MODY type 12 has been reported many times before. According to the literature, the clinical features of our case resemble the reported cases of MODY with *ABCC8* gene mutation (17,47-49). The slight differences between the reported cases suggest that the location of the mutation may be the cause. It should be noted that environmental and epigenetic factors also influence these differences. In addition, neurologic involvement was present in this case, as in previously reported cases. A review of the literature on the role of the sulfonylurea receptor in developing the central nervous system suggests that the two conditions may be related (50). The presence of *ABCC8* gene mutation in developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome with DEND also suggests the same relationship (51). The same variant was previously diagnosed by Özdemir et al. (17). in a Turkish patient, a 13-year-old female with diabetes mellitus, BMI 30.3, fasting serum C-peptide 4.64 ng/mL and HbA1c 12% on oral antidiabetic drug and insulin therapy; the high degree of similarity with the clinical presentation of this case was noteworthy and supported the idea that the variant may be involved. In silico evaluations of this variant, which has a frequency of 0.0006-0.0010 in the community, cannot help determine the exact effect of this "damaging" mutation. More case reports and functional analyses are needed to elucidate their impact.

Another patient with a mutation in the *ABCC8* gene was patient number 31, carrying the c.2539G>A p.A847T variant. The patient, who had a history of diabetes at an early age in 2 previous generations but had hypertriglyceridemia and was overweight and compatible with T2DM, did not receive drug treatment for 3 years since the age of 35 when s/he was diagnosed with diabetes but metformin and gliclazide treatment was started after genetic diagnosis. The *ABCC8* gene is still generally considered by pediatric endocrinologists in the genetic etiology of NDM, but several studies have identified similar *ABCC8* missense mutations with early and late-onset diabetes (52-54).

Case 39 was a 62-year-old patient with diabetes for 30 years whose serum fasting C-peptide level had decreased by approximately 70% from 0.97 ng/mL to 0.27 ng/mL in the last 9 years, with negative autoantibodies. The patient, whose postprandial C-peptide was 2.23 ng/mL and who needed insulin approximately 10 years after the diagnosis, was found to have a c.913G>A; p.V305I missense variant in the *INSR* gene, which was not previously included in the databases and classified as "of uncertain clinical significance" according to ACMG. This was supported by the fact that the father and daughter of the patient with this variant, which was predicted to be "damaging" by in silico analysis programs, had similar early-onset diabetes. In contrast to the conditions associated with insulin response disorders caused by the *INSR* gene, there is a need for more relevant family studies, and case reports in the literature to understand under which disease group this novel variant, which produces an insulin secretion defect phenotype, will be classified in the future (55-57).

A careful review of the clinical features of patients 31 and 39 shows that some features are compatible with the characteristics of MODY and some with the characteristics of T2DM. Furthermore, in addition to the pathogenicity prediction calculation results, the rarity of these variants in large population databases supports that they are pathogenic mutations rather than common benign polymorphisms (58).

Eight mutation-positive cases had parents with diabetes, consistent with OD inheritance of MODY. It was interesting to note that two patients with heterozygote *WFS1* mutations, no: 21 (c.2020G>A; p.G674R and c.1672C>T; p.R558C) and no: 37 (c.1672C>T; p.R558C), had no history of diabetes in their parents. However, these variants were not considered de novo mutations but a penetrance deficiency because both patients had a history of diabetes in their siblings. Especially patient 21 had two variants in the same gene. It was evaluated that this patient, who had no history of diabetes in either parents, might have a phenotype with increased penetrance by inheriting one variant from the mother and one from the father. In the literature, it was previously reported that heterozygous WFS1 mutations like these caused type 2 diabetes–like patterns with early onset (59-61).

Study Limitations

There are some limitations to this study. First, analyzes of existing data were carried out because some of the patients' clinical and laboratory information was not sufficient or accessible. Another limitation is that genetic analysis could not be performed on the family or relatives of the patients with the detected mutations. This situation led to inadequate genotype and phenotype analysis.

Conclusion

In conclusion, genetic variants were identified in 10 (25%) of 40 patients with clinically suspected MODY. Three new variants (*GCK*, c.91A>T;p.Lys31*, *HNF4A*, c.1004G>A;p.G335E and *INSR* c.913G>A;p.V305I) contributed to the literature.

In addition, the findings of this study suggest that clinicians may underutilize genetic testing for MODY and that genetic tests are not sufficiently developed in variant detection.

Our study's results may help better understand the clinical features and genetics of MODY and allow for a more personalized approach to treatment and genetic counselling of patients.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of İstanbul Medeniyet University (no: 2020/0619, date: 26.10.2020). This study was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: As this was a retrospective study based on anonymized data, individual informed consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.U., A.A., M.K., Concept: G.U., Design: G.U., M.K., Data Collection or Processing: G.U., A.A., Analysis or Interpretation: G.U., A.A., M.K., Literature Search: G.U., M.K., Writing: G.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Table: https://d2v96fxpocvxx.cloudfront.net/bd1986e1-0bc1-4f4d-af66-3a184850a065/content-images/5251b73c-5244-470c-a518-fd2be5ff3040.pdf