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Investigation of the Mutation Spectrum in Pediatric Patients with Maturity-Onset Diabetes of Youth (MODY): Experience from a Diagnostic Center in Türkiye

ABSTRACT

Objective: This study was aimed to determine the genetic background of pediatric patients with a clinical diagnosis of maturity-onset diabetes of youth (MODY).

Materials and methods: In this study, MODY-related genes of 80 pediatric patients diagnosed with MODY in Türkiye between January 2016 and January 2022 were investigated using three different large gene panels and next-generation sequencing.

Results: Causal variants were detected in the genes investigated in 16 (20%) of 80 patients included in the study. The *GCK* gene was responsible for the clinical findings in 13 (82%) of 16 patients with a molecular diagnosis, and the *HNF1A, HNF1B,* and *ABCC8* genes in the remaining three patients. This study identified six of the detected genomic variants for the first time in the literature.

Conclusions: MODY is a group of diseases that differ from each other in terms of clinical findings, treatment, progression, genetic etiopathogenesis and incidence. For this reason, genetic analyses using multigene panels will enable accurate identification of MODY subtypes, genetic counseling of patients, guidance to optimal treatment options, and screening of carrier relatives. (Clin Diabetol 2023; 12; 4: 232–238)

Keywords: MODY, monogenic diabetes, multi-gene panel, NGS, pediatric patients

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Introduction

Maturity-onset diabetes of youth (MODY; monogenic diabetes) is a group of monogenic disorders that are mostly seen in young adults, in which insulin resistance is not observed and is inherited as an autosomal dominant.

In these patients, there is typically no autoimmunity against β-cells of the pancreas and these cells continue to function [1]. MODY cases constitute 1–5% of all patients with diabetes [2]. Studies have demonstrated that MODY exhibits a prevalence rate of 0.01 per 100 adults and 0.0033 per 100 children [3, 4]. Furthermore, research indicates that 80% of MODY cases initially receive a misdiagnosis of either type 1 or type 2 diabetes. The interval between misdiagnosis of the cases and determining that they are MODY by genetic analysis was calculated as approximately 15 years [5]. The International Pediatric and Adolescent Diabetes Association (ISPAD) guidelines recommend genetic screening for MODY in the presence of the following

evidence: diagnosis of diabetes before the age of 25, presence of two consecutive generations of diabetes in the family history, loss of β-cell function, absence of β-cell autoantibodies, and persistence of endogenous insulin secretion [6].

Thus far, researchers have successfully identified 14 genes associated with the manifestation of MODY. The *GCK, HNF1A*, and *HNF4A* genes are known to be the primary contributors to the most prevalent forms of MODY. Causal variants within these genes are frequently responsible for the development of MODY. The *GCK* and *HNF1A* genes are responsible for the majority of all MODY cases (30–65%). The *HNF4A* and *HNF1B* genes cause 15% of the cases. The remaining 20% of MODY cases are associated with 10 genes (*BLK, KLF11, NEUROD1, PAX4, KCNJ11, INS, CEL, ABCC8, APPL1*, and *PDX1*) [7].

In this study, genetic analyses of 80 Turkish pediatric patients who met the criteria attributed to MODY by the ISPAD guidelines were performed. It aimed to determine the proportion of individuals diagnosed with molecular genetics and MODY subtypes from these cases whose MODY gene test was performed using the targeted next-generation sequencing (NGS) method.

Materials and methods

Study population

This descriptive study included 80 pediatric patients who underwent MODY genetic analyses in Ankara Diskapi Yıldırım Beyazit Training and Research Hospital, Department of Medical Genetics, between January 2016 and January 2022. These cases were patients who met the MODY criteria defined in the ISPAD guidelines, were clinically diagnosed with MODY by Pediatric Endocrinology physicians, and were referred to the genetics department for molecular confirmation of these diagnoses [8]. Each of these cases, whose pedigree analyses were carefully examined, came from different families, and no consanguinity could be detected between them. The present cohort study involved human participants, and it was conducted considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. Prior to the study, written informed consent was obtained from all participants and this study was approved by an independent Ethics Committee.

Genomic DNA isolation

Genomic DNA of 80 patients was extracted from their peripheral blood using an automated device (Qiagen®, USA). Sequence analyses of all patients were performed by NGS method.

Genetic analysis

Analyses of 20 patients admitted between January 2016 and December 2018 were performed on the Thermo Fisher Scientific Ion S5 System platform and using the Ion PGM™ Hi-Q™ View Sequencing kit (Panel I). With this panel, untranslated regions (UTR) and coding sequences of 18 genes were analyzed (*GCK, HNF1A, HNF4A, HNF1B, ABCC8, GLIS3, ZFP57, KLF11, NEUROD1, FOXP3, PAX4, RFX6, NKX2-2, BLK, NEUROG3, G6PC2, KCNJ11, INSR*). The raw data obtained as a result of sequencing were analyzed with Ion Reporter™ Software and Alamut Visual Biosoftware programs.

Analyses of 23 patients admitted between December 2018 and July 2019 were performed on the Illumina MiSeq® System (Illumina, USA) platform and using the ParSeq-Diabetes kit (Panel II). This panel allowed the analysis of untranslated regions (UTR) and coding sequences of 12 genes (*GCK, HNF1A, HNF1B, INS, HNF4A, BLK, G6PC2, PDX1, INSR, KCNJ11, GLIS3, CEL*). Hotspot regions of *ABCC8, NEUROG3, PAX4, FOXP3, KLF11, NEUROD1, NKX2-2, RFX6, ZFP57, HADH, GLUD1, SLC16A1* genes were also examined by this kit. Variants detected in these genes were analyzed using VariFind™ software.

Analyses of 37 patients admitted between July 2019 and January 2022 were performed on the Illumina MiSeq® System platform and using the MODY MASTR Assay (Multiplicom) kit (Panel III). With this panel, all UTR and coding sequences of seven MODY-related genes (*GCK, ABCC8, INS, HNF1A, HNF1B, HNF4A, KCNJ11*) were examined. The raw data detected in these genes were analyzed via the Sophia DDM® data analysis platform.

Genome interpretation using in silico predictors

This genetic analysis analyzed the coding (exon) and promoter sequences of MODY-related genes, as well as single-base variants and small deletions/duplications at exon-intron boundaries (20 base pairs). Variants with a read depth of at least 30X for each allele were evaluated, based on the reference genome (GRCh37 (h19)). The ACMG (American College of Medical Genetics and Genomics) guidelines were followed in the evaluation of variants [9]. In the analysis of variants, tools such as Mutation Assessor, Fathmm, SIFT, PolyPhen2, DANN, PROVEAN, GERP, MPC, and Mutation Taster were used.

Ethical approval

The Institutional Ethical Committee has approved the present study (2022-128/13).

Informed consent

Informed consent was obtained from all individuals included in this study.

Results

A total of 80 pediatric patients were included in this study, 43 girls (54%) and 37 boys (46%). The mean age of these patients was 13.6 (range 1–18) years. Twenty percent (16/80) of patients had pathogenic and likely pathogenic variants in MODY-related genes. The clinical findings, age of diagnosis, relatives with diabetes mellitus obtained from the pedigree analysis, and genotypic results of these patients receiving molecular diagnosis are summarized in Table 1. The mutation detection rates of the three panels used in the study were 15% (3/20) for Panel I, 30.4% (7/23) for Panel II, and 16.2% (6/37) for Panel III. Of the causative gene variants detected in total by the three panels, 82% (13/16) were in the *GCK* gene, 6% (1/16) were in the *HNF1B* gene, 6% (1/16) were in the *HNF1A* gene, and 6% (1/16) were in the *ABCC8* gene, and all of these variants were heterozygous. Variants of unknown clinical significance (VUS) were detected in the patients' *GCK, BLK, ABCC8*, and *HNF1B* genes in 8.7% (7/80). The 37.5% (6/16) of the causal variants detected in this study were not previously reported in the literature (novel).

Discussion

MODY, which is a genetically and clinically heterogeneous group of diseases, is monogenic diabetes that is observed due to mutations in some autosomal dominant genes that play a role in the development or maintenance of pancreatic β-cells. Many cases of MODY are misdiagnosed as type 1 or type 2 diabetes. In the initial study documented in the literature, where MODY screening was conducted by selecting children with negative autoantibodies from nationwide population-based registries, researchers identified a prevalence rate of 6.5% for MODY. Their research has revealed that about one-third of these cases were also misdiagnosed by clinicians [10]. There are 14 genes associated with MODY cases. Detection of causal variants of these genes in patients with suspected MODY is an important step that covers diagnosis, treatment, and genetic counseling in patients and provides optimal management of the disease. Genetic testing is essential for optimal management of this condition [7]. The most frequently detected causative gene of MODY in our study was *GCK* (82%). The *GCK* gene is responsible for the expression of the enzyme glucokinase, which catalyzes the phosphorylation of glucose to glucose-6-phosphate. Glucokinase is a hexokinase isoenzyme that regulates insulin release in the β-cell of the pancreas in proportion to glucose metabolism and is therefore known as the glucose sensor of the pancreas. *GCK*-MODY (MODY 2) is an autosomal dominant inherited disease caused by heterozygous loss-of-function mutations of the *GCK* gene. Affected individuals have mild HbA1c elevation and mild and stable fasting hyperglycemia from birth [11]. In a large-scale study of Asian individuals with MODY, mutations were most frequently detected in *GCK* (55.3%), followed by *HNF1A* (28.2%), *HNF1B* (9.7%) and *HNF4A* (6.8%) genes [12]. *GCK*--MODY, which is one of the common types of MODY, was observed with the highest prevalence in southern European countries and Türkiye where this study was conducted [13]. Patients are mostly asymptomatic and hyperglycemia levels are noticed in routine examinations. In these patients, insulin secretion and regulation are not completely impaired, and complications that may develop due to diabetes are observed to be quite rare. It has been reported that pharmacological treatment in *GCK*-MODY does not significantly alter HbA1c levels and therefore does not require pharmacological treatment. Due to the increased prevalence of non-proliferative retinopathy in these patients, annual retinopathy screening is recommended, especially in elderly individuals [14]. In this study, the *GCK* gene in 13 of 16 patients whose causative genes were detected, and the *HNF1A, HNF1B*, and *ABCC8* genes in the remaining three patients were causally detected.

The hepatocyte nuclear factor 1-alpha (*HNF1A*) gene has been identified in more than 70% of populations, especially of European origin, leading to MODY3, one of the most common monogenic diabetes types among all MODYs [15]. The *HNF1A* gene plays a role in the regulation of metabolic genes involved in most organs and tissues, especially in the pancreas, liver, intestines, and kidney [15, 16]. *HNF1A* gene mutations also increase the risk of developing type 2 diabetes in many ethnic groups other than MODY3. Liver adenomatosis, which is thought to arise from dysregulated glycolytic signaling pathways and has a risk of transformation into hepatocellular carcinoma, has also been observed in carriers with some causative variants [17]. It has been reported that there is a very heterogeneous picture in MODY3 patients and that environmental and epigenetic factors may have contributed to these findings. MODY3 cases are normoglycemic at birth and present with symptoms such as polyuria, polydipsia, and glucosuria due to progressive loss of β-cell function and decreased insulin secretion. The presence of glycosuria observed in these patients prior to the onset of diabetes is notable. In this type of MODY, where familial symptomatic diabetes is most commonly observed, cases respond well to low-dose sulfonylureas therapy [16]. Another patient analyzed in this study had a causative variant of the *HNF1B* (Hepatic nuclear factor 1B) gene. The *HNF1B* gene plays an important role in embryogenesis and its expression disorders lead to structural and functional

Table 1. The Variants Detected in Patients from the Study Group

Patient ID, age [years], sex	Phenotype (clinical presentation)	Age at diagnosis [years]	Family history of diabetes	Gene	Nucleotide change/AA change	Zygosity	Loc.	ACMG	Func	Pop. Allele Frequency	dbSNP
P4,17/M	Incidentally detected hyperglycemia in medical checkups	14	Father/grand-father	*GCK*	GCK(NM_000162.5):c.544G>A (p.Val182Met)	Het	Ex 5	P	MS	—	rs587780345
P9*,18/F	Bilateral hyperechogenic/ normal-sized kidneys and, incidentally detected hyperglycemia in medical checkups	6	Mother/grand-mother/grand-father/aunt/first cousin	*HNF1B*	HNF1B(NM_000458.4):c.1127C>T (p.Thr376Ile)	Het	Ex 5	LP	MS	—	rs749391290
P10*,9/M	Polyphagia	8	Grandfather	*BLK*	BLK(NM_001715.3):c.549T>A (p.Asp183Glu)	Het	Ex 7	VUS	MS	—	—
P13,17/M	Polyuria, polydipsia, poly-phagia	14	Mother/sister/ grandmother	*GCK*	GCK(NM_000162.5):c.454T>C (p.Phe152Leu)	Het	Ex 4	LP	MS	—	—
P16,18/M	Polyuria, polydipsia	16	Father/uncle	*HNF1B*	HNF1B(NM_ 000458.4): c.1414G>A (p.Val472Ile)	Het	Ex 7	VUS	MS	0.00001043	rs762841746
P17,18/F	Incidentally detected hyperglycemia in medical checkups	12	Mother	*GCK*	GCK(NM_000162.5):c.469G>A (p.Glu157Lys)	Het	Ex 4	P	MS	—	—
P21,16/F	Polyuria, polydipsia	14	Father/grand-mother/5 aunts/2 uncles	*GCK*	GCK(NM_000162.5):c.1256delT (p.Phe419fs)	Het	Ex 10	LP	FS	—	—
P24*,17/F	Incidentally detected hyperglycemia in medical checkups	13	Mother/sister/ her mother's uncle	*GCK*	GCK(NM_000162.5): GCK:c.745G>T (p.Gly249Cys)	Het	Ex7	LP	MS	—	
P26*,9/F	Polyuria, polydipsia, uri-nary incontinence	8	2 aunts	*GCK*	GCK(NM_000162.5):c.46-1G>A (p.?)	Het	Ex2	P	SE	—	—
P31,3/F	Incidentally detected hyperglycemia in medical checkups	2	Grandmother	*GCK*	GCK(NM_000162.5):c.1178T>C (p.Met393Thr)	Het	Ex9	P	MS	—	—
P33*,11/M	Polyuria, polydipsia	10	Mother/first cousin	*GCK*	GCK(NM_000162.5):c.950A>C (p.His317Pro)	Het	Ex8	LP	MS	—	—
P37,11/M	Incidentally detected hyperglycemia in medical checkups	9	None	*ABCC8*	ABCC8(NM_000352.6):c.2694+5G>A (p.?)	Hom	Int22	VUS	SE	—	

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Table 1 cont. The Variants Detected in Patients from the Study Group

Patient ID, age [years], sex	Phenotype (clinical presentation)	Age at diagnosis [years]	Family history of diabetes	Gene	Nucleotide change/AA change	Zygosity	Loc.	ACMG	Func	Pop. Allele Frequency	dbSNP
P50*, 7/M	Polyuria, polydipsia	6	2 first cousins	*GCK*	GCK(NM_000162.5):c.950A>C (p.His317Pro)	Het	Ex8	VUS	MS	—	—
P52,15/M	Polyuria, polydipsia, polyphagia and fatigue	14	Grandmother/ aunt/ 2 second cousins	*HNF1A*	HNF1A(NM_000545.6):c.1340C>T (p.Pro447Leu)	Het	Ex7	P	MS	0.00001204	rs137853236
P56,8/F	Incidentally detected hyperglycemia in medical checkups	7	Brother	*GCK*	GCK(NM_000162.5):c.683C>T (p.Thr228Met)	Het	Ex7	P	MS	0.000003999	rs80356655
P57*,18/F	Weakness, fatigue and tremor	15	Father	*GCK*	GCK(NM_000162.5):c.715C>T (p.Gln239*)	Het	Ex7	P	FS	—	—
P60*,10/M	Incidentally detected hyperglycemia in medical checkups	6	None	*GCK*	GCK(NM_000162.5):c.112C>T (p. p.Gln38*)	Het	Ex2	P	FS	—	rs878853246
P61*,9/F	Incidentally detected hyperglycemia in medical checkups	7	Father/second cousin	*ABCC8*	ABCC8(NM_000352.6):c.2011G>A (p.Asp671Asn)	Het	Ex14	VUS	MS	—	—
P64,15/M	Lethargy and dizzy	13	Father/grandfather/ 2 uncles	*BLK*	BLK(NM_001715.3):c.1075C>T (p.Arg359Cys)	Het	Ex11	VUS	MS	0.0008040	rs146505280
P66,14/F	Polyuria, polydipsia, weakness and fatigue	12	Mother/sister	*ABCC8*	ABCC8(NM_000352.6):c.1261G>A (p.Val421Ile)	Hom	Ex8	VUS	MS	—	—
P69*,18/F	Polyuria, muscle spasms, and progressive weight loss	13	Mother	*ABCC8*	ABCC8(NM_000352.6):c.1332G>T (p.Gln444His)	Het	Ex 8	P	MS	—	—
					ABCC8(NM_000352.6):c.3242C>T (p.Thr1081Met)	Het	Ex26	VUS	MS	0.00000398	rs764005234
P77,12/M	Incidentally detected hyperglycemia in medical checkups	10	Mother/sister/ grandmother/3 aunts/uncle	*GCK*	GCK(NM_000162.5):c.506A>G (p.Lys169Arg)	Het	Ex5	LP	MS	—	—
P80,13/F	Incidentally detected hyperglycemia in medical checkups	9	Father/grandmother/aunt	*GCK*	GCK(NM_000162.5):c.106C>T (p.Arg36Trp)	Het	Ex2	P	MS	0.00001414	rs762263694

*patient with novel mutation; AA — aminoacid; Ex — exon; F — female; FS — frameshift; Func — function; Het — heterozygous; Hom — homozygous; Int — intron; M — male; MS — missense; P — pathogenic; Pop. Allele Frequency — population allele frequency (gnomAD)SE — splice effect; VUS — variant of uncertain significance

abnormalities in organs such as the urogenital system, liver, and pancreas. In the literature, *HNF1B* has been reported as the causative gene in a phenotypically heterogeneous and multisystemic disease called "renal cysts and diabetes syndrome (RCAD)". Renal anomalies observed in RCAD cases are cystic renal disease and collecting system anomalies, in order of frequency [18]. *HNF1B*-MODY (MODY5) is responsible for less than 5% of all MODY cases. Phenotypic heterogeneity is observed among cases, even in family members carrying the same causative variant [19]. The hypoplasic pancreas observed in patients causes dysfunction in β-cells and a decrease in insulin secretion. In cases with HNF1B mutation, diabetes is observed in nearly 50% of individuals, and it is characterized by a combination of insulin resistance and dysfunction of β-cells. Hypomagnesemia, hypokalemia, hypocalciuria, hepatic dysfunction, microvascular complications, and low birth weight have been reported in these patients [20]. Early insulin therapy is needed because MODY5 cases do not respond well to sulfonylurea therapy. These patients are at risk of experiencing various extrapancreatic anomalies, particularly affecting the renal system. It has been reported that most of the mutation carriers in the fourth decade develop renal dysfunction and some of them progress to renal failure. Therefore, it is recommended that diagnosed cases be included in a periodic screening program for possible renal anomalies and nephropathy management should be provided [21].

In another patient in the study, the *ABCC8* gene was causally detected. The adenosine triphosphate (ATP)-dependent potassium channel, which has an important function in regulating insulin secretion, is a hetero-octamer structure composed of potential sulfonylurea receptor1 (SUR1) regulatory subunits. Loss-of-function mutations of the *ABCC8* gene, which is responsible for coding SUR1, cause neonatal diabetes, while gain-of-function mutations can cause severe neonatal hypoglycemia [22]. In studies conducted in large cohorts with diabetes from different geographies in the literature, the prevalence of *ABCC8* causative gene has been reported to be around 0.5–1.5% [23]. The *ABCC8* gene is responsible for the MODY 12 subtype, and a highly heterogeneous phenotype can be observed, such as needing insulin therapy and only having impaired glucose tolerance, even in family members carrying the same mutation. Due to the variability of clinical presentations resulting from different causative variants in the *ABCC8* gene, it is important to note that the appropriate treatment may not be uniform for all patients affected by these variants. However, the treatment of these patients with sulfonylurea has been successful in over 90% [24].

MODY, which has been associated with loss of function of pancreatic β-cells, has been associated with 14 genes with an autosomal dominant inheritance pattern. The diagnosis of MODY, which encompasses a highly heterogeneous group of diseases in terms of genetics and clinical aspects, presents a significant challenge for clinicians. As a result, these patients are frequently misdiagnosed initially as having type 1 or 2 diabetes. There are differences in the prediction of treatment protocols and disease course not only for type 1 and type 2 diabetes but also for each subgroup of MODY patients. Therefore, making the correct diagnosis in patients will make it possible to avoid inappropriate treatment protocols (such as the well-known long-term insulin therapy in type 1 diabetes). Considering the burden that the wrong treatment options may cause in terms of health and economy, genetic testing is necessary in order to make the correct diagnosis in these cases.

In this study, we aimed to investigate the genetic backgrounds in cases with a clinical diagnosis of MODY in accordance with the ISPAD guidelines. In the genetic analysis of 80 patients included in this study, using large gene panels, 16 (20%) cases received the molecular diagnosis. As a result of the analysis, the *GCK* gene was found to be responsible for the majority of all cases, and the *HNF1B, HNF1A,* and *ABCC8* genes were determined as causative in the remaining three cases. Several factors, including the design of genetic analyses conducted on the MODY patient group, the extent of genes investigated, and the technical capabilities, can contribute to the variability in research data within the same and different populations. Nevertheless, consistent with previous studies conducted in our population, our study also found GCK to be the most frequently identified causative gene [25].

Our study has a few limitations. Firstly, it was planned retrospectively, which may introduce inherent biases. Additionally, the study was conducted with a relatively small number of patients, which may limit the generalizability of the findings. Furthermore, due to the nature of the study design, detailed information regarding the clinical findings and treatments of the patients could not be included. Other limitations of the study are the use of three different large gene panels in the genetic analysis, the screening of different mutations at different times, and the inability to reach the segregation analysis targets in relatives with the same phenotype for the detected mutations.

Conclusions

In conclusion, recent advances in genetics enable the molecular identification of specific subtypes of the

disease in many MODY cases, enabling the prediction of disease progression and the planning of an individualized treatment protocol. Molecular diagnosis not only of the patient but also of the relatives of the carrier patients in the preclinical phase will be beneficial in the implementation of optimal treatment options and thus in preventing the development of diabetes-related complications. Although many genetic studies from different ethnic groups and populations have been reported in the literature, further studies are needed to understand the phenotype and genotype relationship observed in MODY patients and elucidate the disease's complex and highly heterogeneous nature.

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Conflict of interest

Authors state no conflict of interest.

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