3(2): 28-0xx; Jun 2024
Pediatric Academic Case Reports
DOI: 10.61107/pacr.2024.109

Cade Report

MODY 10 Diagnosis in a Case Presenting with Diabetic Ketoacidosis: Novel Insulin Gene Variant

Diabetik Ketoasidoz ile Başvuran Bir Vakada MODY 10 Tanısı: Yeni İnsülin Geni Varyantı

Sevim Onguner[1], Berna Eroğlu Filibeli[1], Eren Er[1], Taha Reşit Özdemir[2], Bumin Nuri Dündar[3]

[1]*Tepecik Training And Research Hospital, Pediatric Endocrinology, İzmir, Türkiye*
[2]*Health Sciences University İzmir Faculty Of Medicine , Medical Genetics, İzmir, Türkiye* [3]*İzmir Katip Çelebi Faculty Of Medicine, Pediatric Endocrinology, İzmir, Türkiye*

ABSTRACT

Maturity onset diabetes of the young (MODY) accounts for 1-2% of all diabetes.(1) An 11-year-old female girl was diagnosed with diabetes with typical diabetes symptoms, and laboratory findings of diabetic ketoacidosis and multiple-dose insulin therapy were started. In the follow-up, she had diabetes autoantibody negativity and a MODY panel was applied. It was reported that a novel heterozygous variant [(NM_000207.3: c.76G>A (p.Val26Met) (Exon2)] in the insulin (2) gene, causing MODY 10, one of the rare types of MODY. Her parents were negative for the variant, so the variant was de-nova. MODY 10 can cause diabetic ketoacidosis, and patients can be misdiagnosed with type 1 diabetes. Screening for variations in identified MODY genes should be kept in mind in patients who require small insulin doses and have negativity for diabetes autoantibodies.

Keywords: *MODY, INS gene, diabetic ketoacidosis variation*

ÖZET

Gençlerin erişkin başlangıçlı diyabeti (MODY) tüm diyabetlerin yaklaşık % 1-2'sini oluşturur.(1) Olgumuz insulin bağımlı diyabet tanısı ile izlenirken 6 aylık takibinde diyabet otoantikor negatifliği nedeniyle olgumuzda MODY paneli çalışılmıştı. MODY'nin nadir tiplerinden biri olan MODY tip 10 neden olan yeni bir heterozigot varyantı [NM_000207.3:c.76G>A(p.Val26Met)(Exon2)] insülin (2) geninde hastamızda de novo olarak tanımlandı. İnsülin bağımlı, diyabet otoantikorları negatif olan ancak sınıflandırılmamış atipik diyabeti olan hastalarda tanımlanmış MODY genlerindeki varyasyonlar için tarama yapmak akılda tutulmalıdır.

Keywords: *MODY, INS geni, diyabet, varyasyon*

INTRODUCTION

Maturity onset diabetes of the young (MODY) accounts for 1-2% of all diabetes. It is caused by autosomal dominant variations, and 14 MODY subtypes have been identified to date. One of the rare types of MODY, MODY

Received: 17.10.2023 · **Accepted:** 09.01.2024 · **Published:** 12.05.2024

Correspondence / Yazışma: Sevim Onguner · Tepecik Eğitim ve Araştırma Hastanesi, Pediatrik Endokrinoloji Bölümü, İzmir, Türkiye · songuner.so@gmail.com

Cite this article as: Onguner S, Eroğlu Filibeli B, Er E, Özdemir TR, Dündar BN. MODY 10 Diagnosis in a Case Presenting with Diabetic Ketoacidosis: Novel Insulin Gene Variant. Pediatr Acad Case Rep. 2024;3(2):24-7.

10, is caused by heterozygous insulin (2) gene variations. MODY 10 is caused by an *INS* gene mutation, and more than 50 mutations have been identified. Heterozygous *INS* mutations may cause neonatal diabetes mellitus (DM) and MODY phenotypes with the same variations, even within the same family. In this report, an 11-year-old girl who presented with diabetic ketoacidosis and was diagnosed with MODY type 10 by detecting novel heterozygous variation in the *INS* gene is presented.

CASE REPORT

An 11-year-old girl was applied to the emergency department with complaints of sore throat and cough for a week. She had polydipsia, polyuria and weight loss of 2 kg, which had been going on for two months. She was born with a second-degree consanguineous marriage at 39th gestational weeks and with a birth weight of 3250 g. There was no history of hypo/hyperglycemia in the newborn stage, no known family history of DM. In the physical examination, weight was 26 kg (-2.34 SDS), height was 140 cm (-1.23 SDS), puberty stage was Tanner 2, had Kussmaul respiration and dehydrated appearance. In the blood gas pH: 7.06 (7.35-7.45), pCO2: 24 mmHg (35-45 mmHg), HCO3: 9.2 mmol/L (22-26 mmol/L) and serum glucose: 457 mg/dl (60-200 mg/dl), C-peptide: <0.01 µg/L (0.9-7.1), HbA1c: 17% (4-6%), urine ketone +++, anti-insulin and GAD autoantibodies were negative (Table 1). Since the patient was positive for COVID PCR, she was followed up in the infection unit, received an online basic diabetes education program, and was discharged with 1.2 unit/kg/day multiple dose insulin therapy. In the follow-up, genetic analysis was performed for MODY since diabetes autoantibodies (anti-insulin and GAD autoantibodies) were negative.

Methods

Genomic DNA was extracted from peripheral blood leukocytes of the patient and her parents using MagNA Pure LC DNA Isolation Kit I (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocol. The MODY NGS Panel (Celemics, Inc., Seoul, Korea) was used for the identification of variants in the coding regions and the exon-intron boundaries of the MODY-associated genes, including GCK, HNF1A, HNF1B, HNF4A, INS. Targeted NGS was performed on an Illumina MiSeq NGS System (Illumina Inc., San Diego, CA, USA) using the MiSeq Reagent Nano Kit v2 (500 cycles) (Illumina Inc., San Diego, CA, USA). The raw data obtained by the NGS method was analyzed using 'SEQ' variant analysis software (Genomize, İstanbul, Turkey) according to the reference genome of GRCh37(h19). The filtered variants were evaluated according to the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines recommendations. The variant was found in the INS gene as NM_000207.3:c.76G>A(p.Val26Met)(Exon2) Heterozygous state. Sequencing analysis of her parents was normal for the relevant variant. Thus, it was evaluated as 'de novo'. It was not found in databases (dbSNP, ClinVar, population databases). It was evaluated as a 'variant of unknown significance-VUS' according to the Varsome platform.

Table 1. Laboratory Results

Laboratory:	
Liver/Kidney Function Tests	AST: 18 U/L(N, 0-35) ALT: 9 U/L(N, 0-35) Urea: 17 mg/dl (N, 10-38) Creatinin: 0.7 mg/dl (N, 0.5-1.2)
Thyroid Function Tests	TSH: 1.77 mIU/L (N, 0.34-5.6) T4: 0.95 ng/dl(N, 0.61-1.06) T3: 6.29 ng/L (N, 2.59-4.3)
Anti Glutamic Acid Decarbocylase Antibody **Anti Insulin Antibody**	0.42 IU/ml(N, <10) 2.9 U/ml (N, <10)
HbA1c	17% (N, 4-6%)
Glucose	90 mg/dl (N, 60-100)
C-peptid	<0.1µg/L (N, 0.9-7.1)
Insulin	13.9 mU/L (N,1.9-23)
Celiac Autoantibodies	Tissue transglutaminase IgA: 0.2 RU/ml (<10) Tissue transglutaminase IgG: 1.7 RU/ml (<10)
Urinary Test	Ph:5 Density:1029 (N, 1010-1030) Protein:+2 Glucose:+4 Ketone:+3

Results and clinical follow-up

A heterozygous variant of c.76G>A(p.Va126Met) was detected in the *INS* gene. The variant has not been reported in databases before; it is a novel variant and considered as a variant of unknown significance. As a result of the segregation analysis from the mother and father, the mutation was shown to be de-nova (Figure 1). The patient has followed up with the diagnosis of MODY 10 and had a mean HbA1c of 6.8% in the last one

year with bilateral metabolic cataract and without other microvascular and macrovascular complications.

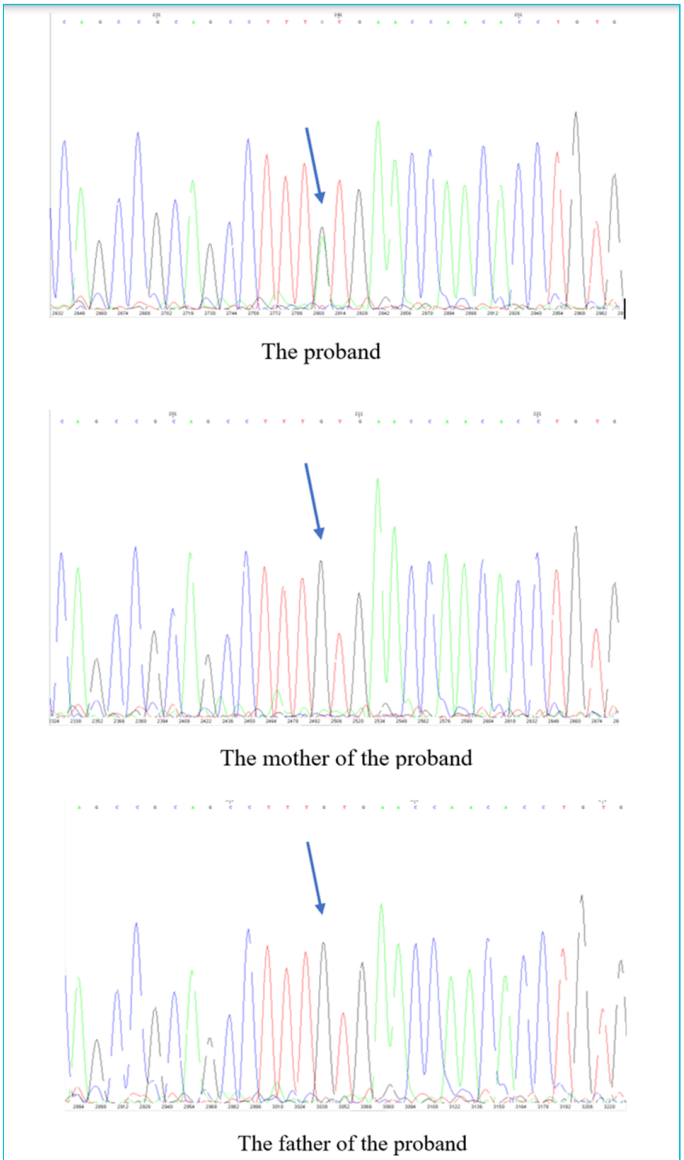

Figure 1. Electropherograms of family members

DISCUSSION

MODY 10 is caused by *INS* gene variation. The *INS* gene is located on chromosome 11p 15.5 and is a gene that directly encodes insulin protein, containing three exons and two introns. Exon 2 and exon 3 are the main peptide-coding regions of insulin. Exon 2 is the coding region of the signal peptide B chain and parts of C-peptides.(3) A wide spectrum of clinical manifestations has been reported in *INS* gene variations even within a single family, especially considerable differences in residual β-cell function.(4) Our patient was at a young age and had typical hyperglycemia symptoms, severe hyperglycemia with ketoacidosis, and lean body habitus with a body mass index of 15.06 kg/m^2. She had no positive autoimmune antibody of diabetes and no previous history of family members with DM. All the above points drove us away from the diagnosis of type 1 and type 2 diabetes mellitus. Although there was no positive family history for diabetes, no record of hypo/hyperglycemia and neonatal diabetes, a genetic MODY panel was applied due to negative autoantibodies of diabetes. A heterozygous novel variant [NM_000207.3:c.76G>A(p.Val26Met)(Exon2)] was detected in the *INS* gene. In Norwegian brief report *INS* mutation c.163C>T (R55C) found in a girl who at 10 years of age presented with ketoacidosis and insulin dependent, anti GAD and insulinoma-associated antigen-2 (IA-2) antibody-negative diabetes. (5)Her fasting C-peptide was detectable (500 pmol/l) and she was insulin dependent from the time of diagnosis; like our case, her recent insulin requirement and Hba1C were 0.72 units/kg/day and 8.0% respectively (5). In 2019, Xiao et al.(4) reported a 23-year-old proband having *INS* exon three frameshift mutation with familial diabetes in three generations who was diagnosed at 15 years old. The proband was diagnosed with hyperglycemia in 2009 due to typical diabetic symptoms without signs of diabetic ketoacidosis and was treated with metformin and gliclazide. After two years from the diagnose, she attempted to hospital again with a complain of blurred vision and like our case, she also got the diagnose of metabolic cataract (4). Insulin therapy was then suspended. The mother of the child suffered from a fundus hemorrhage and retinal detachment at the age of 23. Metabolic cataracts of the proband and her mother are likely secondary to hyperglycemia(4). The clinical manifestation of the mother of the child was severe, similar to type 1 diabetes mellitus. Since being diagnosed with diabetes at one year of age, she has been receiving insulin treatment. The result suggests that although both have the same variant, the clinical phenotype of the child was significantly different from that of the child's mother.

Our patient also had blurred vision in the 1.5 years policlinic follow ups and diagnosed bilateral metabolic cataract. After this diagnose bilateral intraoculer lens implantation was made by ophtalmologists to our case. The exact etiology of cataract formation in diabetes remains to be elucidated(6). Diabetes is an established risk factor for the occurrence of cataracts, although the exact etiology of cataract formation in diabetes remains unknown. In animal models, excess glucose in the lens is converted to sorbitol by aldose reductase(7). Accumulation of sorbitol leads to osmotic stress; however, in humans, the sorbitol levels do not rise high enough to cause significant damage. Additional proposed mecha–

nisms include NADPH depletion leading to oxidative stress or non-enzymatic protein glycation in the lens(8). Complications of MODY 10, such as retinopathy, neuropathy, and microalbuminuria, have been reported. However, to our knowledge, obesity, hypertension, and hyperlipidemia, have not been reported in the literature. The treatment of MODY 10 is similar to that of other types of MODY, mainly by diabetes diet, exercise, and insulin (3) Among patients with MODY10 who have the same variation in the same family, most of the clinical phenotypes have high reproducibility, and a few of them can show a significant gap (9). It is reported in studies that the R46Q mutation is carried in two families from Norway and Czechoslovakia. In the Norwegian family, the proband with the R46Q mutation, the father and the aunt of the proband developed diabetes at 20, 18, and 17 years, respectively. The proband and the aunt of the proband can control the disease through diet treatment only, while the father of the proband was initially treated with diet treatment and began to take oral sulfonylureas 20 years later. [3] Clinical heterogeneity in terms of the age at diagnosis, manifestations and therapeutic options are evident in MODY types.

In conclusion, in cases with Type 1 Diabetes Mellitus phenotype and diabetic ketoacidosis with negative autoantibodies, analyzing MODY genes with the help of panels for definitive diagnosis is significant. Thus, the definitive diagnosis of the patients can be established, undiagnosed family members can be diagnosed, and the genotype-phenotype characteristics of the disease can be clarified.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

Financial Disclosure / Finansal Destek

The authors received no financial support for the research and/or publication of this article.

REFERENCES

1. Flannick J, Johansson S, Njølstad PR. Common and rare forms of diabetes mellitus: towards a continuum of diabetes subtypes. Nature Reviews Endocrinology 2016; 12(7): 394-406.
2. Bank RA, Robins SP, Wijmenga C, et al. Defective collagen crosslinking in bone, but not in ligament or cartilage, in Bruck syndrome: indications for a bone-specific telopeptide lysyl hydroxylase on chromosome 17. Proceedings of the National Academy of Sciences. 1999; 96(3): 1054-8.
3. Lei S-Q, Wang J-Y, Li R-M, et al. MODY10 caused by c. 309-314-del CCAGCT insGCGC mutation of the insulin gene: a case report. American Journal of Translational Research 2020; 12(10): 6599.
4. Xiao X, Liu L, Xiao Y, et al. Novel frameshift mutation in the insulin (INS) gene in a family with maturity onset diabetes of the young (MODY). Journal of Diabetes 2019; 11(1): 83.
5. Molven A, Ringdal M, Nordbø AM, et al. Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. Diabetes 2008; 57(4): 1131-5.
6. Wasserman H, Hufnagel RB, Miraldi Utz V, et al. Bilateral cataracts in a 6-yr-old with new onset diabetes: a novel presentation of a known INS gene mutation. Pediatr Diabetes 2016; 17(7): 535-9.
7. Varma SD. Aldose reductase and the etiology of diabetic cataracts. Curr Top Eye Res 1980; 3: 91-155.
8. Obrosova IG, Chung SS, Kador PF. Diabetic cataracts: mechanisms and management. Diabetes Metab Res Rev 2010; 26(3): 172-80.
9. Piccini B, Artuso R, Lenzi L, et al. Clinical and molecular characterization of a novel INS mutation identified in patients with MODY phenotype. European journal of medical genetics 2016; 59(11): 590-5.