



A family with novel homozygous deletion mutation (c.1255delT; p.Phe419Serfs*12) in the glucokinase gene, which is a rare cause of permanent neonatal diabetes mellitus

Kalıcı neonatal diabetes mellitusun nadir bir nedeni olan glukokinaz geninde yeni homozigot delesyon mutasyonu saptanan aile (c.1255delT; p.Phe419Serfs * 12)

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The known about this topic

Mutations with loss of heterozygous function in the glucokinase gene cause GCK-MODY with mild fasting hyperglycemia. However, homozygous inactivating mutations in the GCK gene have been demonstrated to be an infrequent cause of permanent neonatal diabetes mellitus (PNDM) with an autosomal recessive inheritance.

Contribution of the study

Homozygous inactivating mutations in the GCK gene should be considered as a cause of PNDM in families with consanguineous marriage and a history of diabetes.

Abstract

Heterozygous inactivating mutations in the glucokinase gene cause the mildest form of maturity-onset diabetes of the adolescents. However, homozygous or compound heterozygous mutations in the glucokinase gene are a rare cause of permanent neonatal diabetes mellitus. Herein, we present the case of a male child with permanent neonatal diabetes mellitus whose mutational analysis revealed a novel homozygous deletion mutation in the glucokinase gene. The male proband of Turkish ancestry from consanguineous parents was born at 37 weeks gestation with a birth weight of 1870 g (<3rd percentile). Hyperglycemia developed during the first postnatal day and diabetes-related autoantibodies were negative. He was put on insulin on the first day of life. Insulin has never been discontinued since then. The mother was aged 35 years and had gestational diabetes. The father and the two brothers had impaired fasting glucose. Both parents and brothers were heterozygous for this mutation.

Keywords: GCK-MODY, glucokinase gene mutation, permanent neonatal diabetes mellitus

Öz

Glukokinaz genindeki heterozigot inaktive edici mutasyonlar, gençlikte ortaya çıkan erişkin tip diyabetin en hafif formuna neden olur. Bununla birlikte, glukokinaz genindeki homozigot veya bileşik heterozigot mutasyonların kalıcı neonatal diabetes mellitusun nadir bir nedeni olduğu gösterilmiştir. Burada, mutasyon analizi glukokinaz geninde yeni bir homozigot silme mutasyonunu ortaya koyan kalıcı neonatal diabetes mellituslu bir erkek çocuk olgusunu sunuyoruz. Aralarında akrabalık olan Türk anne- babanın erkek çocuğu 37. gebelik haftasında 1870 gr (<3 persentil) olarak doğdu. Postnatal 1. gün hiperglisemi gelişti ve diyabet ile ilişkili otoantikorlar negatifti. Yaşamın ilk gününde insülin başlandı. İnsülin o zamandan beri hiç kesilmedi. Annesi 35 yaşındaydı ve gebelik diyabeti vardı. Babası ve iki kardeşi de bozulmuş açlık glukozuna sahipti. Ebeveynler ve kardeşler bu mutasyon için heterozigottu.

Anahtar sözcükler: GCK-MODY, glukokinaz gen mutasyonu, kalıcı neonatal diabetes mellitus

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Introduction

Neonatal diabetes mellitus (NDM) is a rare form of diabetes characterized by hyperglycemia, dehydration, and ketoacidosis, which begins in the first six months of life (1). Its incidence was reported to range from 1/90 000 to 215 000 live births in previous studies (2, 3). Neonatal diabetes mellitus is classified as transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM). Although TNDM, which is responsible for 50–60% of cases with neonatal diabetes, enters remission within three months after diagnosis, PNDM is a lifelong disease without remission. Permanent neonatal diabetes mellitus is a genetically heterogeneous disease and causative mutations have been identified in 20 different genes to date. These genes are *KCNJ11*, *ABCC8*, *INS*, *FOXP3*, *GCK*, *PDX1*, *PTF1A*, *EIF2AK3*, *SLC2A2*, *GATA6*, *SLC19A2*, *WFS1*, *NEUROD1*, *NEUROG3*, *RFX6*, *WFS1*, *NKX2-2*, *MXN1*, *IER3IP1*, and *GLIS3* (4). In European and Japanese populations, mutations in the *KCNJ11* and *ABCC8* genes encoding for Kir6.2 and SUR1 subunit proteins of the pancreatic adenosine triphosphate (ATP)-sensitive potassium channel (K-ATP) are the most prevalent cause of PNDM. On the other hand, in populations where the frequency of consanguineous marriages are high, rare genetic causes of PNDM such as homozygous or compound heterozygous mutations in the *EIF2AK3*, *INS*, and *GCK* genes constitute a large part of the cases (5). Here, we report a rare case of PNDM caused by a novel homozygous inactivating mutation in the *GCK* gene.

Case

The male proband of Turkish ancestry from consanguineous parents was born at 37 weeks gestation by cesarean section because of poor fetal growth, with a birth weight of 1870 g (<3rd percentile). Due to hyperglycemia and respiratory distress that developed during the first postnatal day,

the infant was followed up in the neonatal intensive care unit. The mother was aged 35 years and had gestational diabetes. The serum glucose measured at the 13th hour of the newborn was 362 mg/dL, the concurrent serum insulin level was 0.20 mIU/mL, and the C-peptide value was <0.10 ng/mL. Intravenous insulin therapy was initiated at a dosage of 0.03 U/kg/hour in the patient who had no ketoacidosis, and diabetes-related autoantibodies were negative. A physical examination revealed moderate dehydration with tachycardia but no dysmorphic findings were found. The insulin requirement, which was 0.02 U/kg/day in the first month, increased to 0.8 U/kg/day when the patient was aged 2 months. In the following period, insulin pump therapy was started and insulin requirement was determined as 0.6 U/kg/day. The patient is now aged 3 years and receives 0.53 U/kg/day insulin with an insulin pump. The glycated hemoglobin (HbA1c) value of the patient is 7.5% at this time. Mental-motor development is normal and he is within the 50–75th percentiles for both weight and height.

The postpartum fasting blood glucose of the mother who used insulin treatment during pregnancy was 116 mg/dL; the postprandial blood glucose was 185 mg/dL and the HbA1c value was 5.8% (6.5 before the insulin treatment). The proband had two brothers, one of whom was aged 14 years and the other was aged 11 years. Another brother died in the first days after birth, no definite knowledge of why he died was determined, but no abnormality was detected in the glucose values. According to the results of the blood values, it was established that the father and the two brothers who also had glucose intolerance. Data on the glucose levels of family members are shared in Table 1.

The proband was diagnosed as having PNDM; the coexistence of parental consanguinity and the family history of mild hyperglycemia directed us to seek for mutations in the *GCK* gene. After obtaining written informed consent

Table 1. Clinical parameters of family members

	Age	FPGL (mg/dL)	PGL at 120 th min (mg/dL)	OGTT	HbA1C	Mutation
Proband's mother	35	116	185	IGT	5.8	c.1255delT heterozygous
Proband's father	36	124	137	Normal	6.6	c.1255delT heterozygous
Proband's brother	14	127	157	IGT	6.4	c.1255delT heterozygous
Proband's brother 2	11	119	148	IGT	6.2	c.1255delT heterozygous

FPGL: Fasting plasma glucose level; PGL: Plasma glucose level; OGTT: Oral glucose tolerance test; IGT: Impaired glucose tolerance

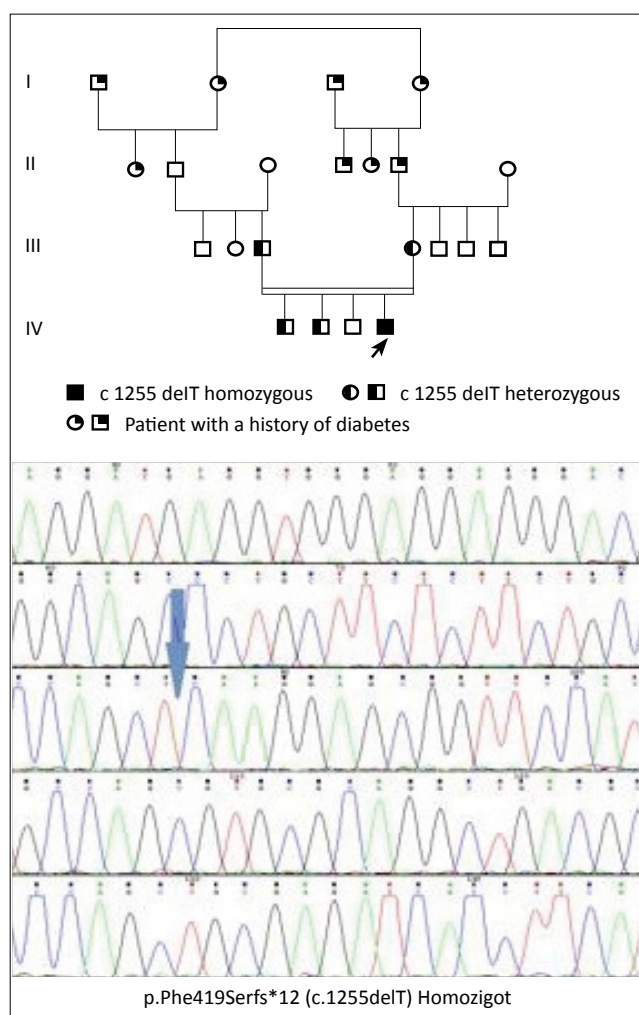


Figure 1. Family pedigree and nucleotide sequence of the GCK gene showing a homozygous deletion mutation (c.1255delT; p.Phe419Serfs*12)

from the parents of the patient, peripheral blood samples were collected in tubes containing EDTA for DNA isolation from all family members. All of the coding exons and intron-exon boundaries of the GCK gene were amplified using polymerase chain reaction (PCR) with specific primers, and then Sanger sequencing was performed to all the coding regions and exon-intron boundaries of the GCK gene of the proband. The proband was found to be homozygous for a novel deletion mutation (c.1255delT; p.Phe419Serfs*12) in the GCK gene. In other family members with mild hyperglycemia, GCK gene analysis was performed and both parents and brothers were determined to be heterozygous for this mutation (Fig. 1). Informed consent was obtained from patients' parents who participated in this study.

Discussion

Here, we describe a patient born to consanguineous parents who developed PNDM associated with a homozygous

inactivating mutation in the GCK gene. The proband's mother had gestational diabetes. His father and the two brothers also had impaired fasting glucose. Both parents and brothers were detected as having a heterozygous inactivating mutation in the GCK gene. Mutations with loss of heterozygous function in the glucokinase gene leads to GCK-MODY, the clinical feature of which is mild fasting hyperglycemia. These patients do not usually require medical therapy except for during pregnancy. However, homozygous or compound heterozygous mutations in the GCK gene are a rare cause of PNDM with an autosomal recessive inheritance (6). Patients with PNDM caused by homozygous inactivating mutation in the GCK gene require life-long insulin therapy because GCK is a key factor in insulin expression with glucose stimulation. The absence of total GCK in infants with this mutation causes severe hyperglycemia and sometimes ketoacidosis in the first days of life. Subcutaneous insulin injections are frequently administered in the treatment of PNDM. However, the absorption of the injected insulin can be unpredictable in newborns with little subcutaneous fat tissue and hypoglycemia is encountered as a serious problem. Insulin pump therapy provides more stable glucose levels by delivering very low and variable amounts of insulin in patients with NDM with variable oral intake. In the current case, hyperglycemia developed within the first day of life. Following intravenous insulin infusion, treatment with neutral protamine Hagedorn (NPH) insulin was introduced. Due to wide fluctuations in blood glucose levels despite strict follow-up, his insulin regimen was switched from subcutaneous insulin injections to continuous subcutaneous insulin infusion in the 3rd month of life. This treatment method reduced the fluctuations in blood glucose. As the daily insulin requirement of the infant was low, infusion set occlusions occurred in the first three months of treatment, but this problem resolved with increasing insulin doses over time and good glycemic control was achieved.

Mutations in the KCNJ11 and ABCC8 genes are responsible for most cases of PNDM, and homozygous inactivating mutations of the glucokinase gene are only detected in low percentages. McCarthy et al. (7) demonstrated that the GCK gene was responsible for 3% of PNDM. In other work performed for the genetic etiology of Arab and British cohorts, it was shown that the GCK gene was responsible for 5.7% of PNDM in Arabic patients and 1.3% in British patients (8). In a cohort of 22 patients with NDM in Turkey, six patients with a homozygous GCK mutation were detected and they found the annual incidence of PNDM as one in 48 000 live births (9). According to the results of the study, GCK-PNDM constitutes more than 25% of NDM cases in Turkey and this was the highest reported rate for GCK-PNDM to date. The study was conducted in

the southeastern Anatolia region where consanguineous marriage is common. Interestingly, in a recent study conducted in Saudi Arabia, where there is a high degree of consanguineous marriage, GCK-PNDM was not detected (10). Accordingly, we can say that from all these data, the frequency of the genes causing neonatal diabetes varies according to populations. Different gene panels can be designed according to etiology in different populations or the priority order of the genes to be run may vary.

In conclusion, when the GCK mutation is detected, other family members also need to be screened. Homozygous inactivating mutations in the GCK-gene should be considered as a cause of PNDM in families with consanguineous marriage and a history of diabetes. Insulin pump therapy may be preferable for infants with NDM because it is more physiologic than subcutaneous insulin injections and provides more stable glucose levels.

Informed Consent: Informed consent was obtained from the parents of the patient who participated in this study.

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