CASE REPORT

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Neonatal Diabetes, Congenital Hypothyroidism, and Congenital Glaucoma Coexistence: A Case of *GLIS3* Mutation

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What is already known on this topic?

Neonatal diabetes and congenital hypothyroidism syndrome is a rare condition caused by homozygous or compound heterozygous mutations in the *GLIS3* gene, with 22 patients reported so far. Small for gestational age infant, congenital glaucoma, polycystic kidney disease, cholestatic hepatic fibrosis, pancreatic exocrine insufficiency, developmental delay, dysmorphic facial findings, sensorineural deafness, osteopenia, and skeletal anomalies are accompanying findings in these patients.

What this study adds?

Herein, one of the oldest surviving *GLIS3* mutation cases reported to date, with both cardinal findings of neonatal diabetes and congenital hypothyroidism syndrome is presented. The patient is the second case with a homozygous exon 10-11 deletion and is also the second known Turkish case.

Abstract

Neonatal diabetes and congenital hypothyroidism (CH) syndrome is a rare condition caused by homozygous or compound heterozygous mutations in the *GLIS3* gene. Small for gestational age, congenital glaucoma, polycystic kidney disease, cholestatic hepatic fibrosis, pancreatic exocrine insufficiency, developmental delay, dysmorphic facial features, sensorineural deafness, osteopenia, and skeletal anomalies are other accompanying phenotypic features in the 22 cases described so far. We present a male patient with neonatal diabetes, CH, congenital glaucoma, developmental delay, and facial dysmorphism. During the patient's 17-year follow-up, no signs of exocrine pancreatic insufficiency, liver and kidney diseases, deafness, osteopenia, and bone fracture were observed. A homozygous exon 10-11 deletion was detected in the *GLIS3* gene. We report one of the oldest surviving *GLIS3* mutation case with main findings of neonatal diabetes and CH syndrome to contribute to the characterization of the genotypic and phenotypic spectra of the syndrome.
Keywords: *GLIS3*, neonatal diabetes, congenital hypothyroidism, congenital glaucoma

Introduction

Neonatal diabetes mellitus (NDM) is an extremely rare cause of monogenic diabetes in which persistent hyperglycemia usually occurs in the first six months of life. Although the frequency is reported to be 1 in 90,000-300,000 in different studies, it is suggested that it may be at least 3-10 times more common in the Middle East region, where consanguineous marriage is more common (1,2). Syndromic NDM constitutes 10% of this rare patient group (1). NDM with congenital hypothyroidism (CH) (MIM#610199) is a rare condition caused by homozygous or compound heterozygous mutations in the GLI-similar 3 (*GLIS3*) gene. The *GLIS3* transcription factor was first identified in 2003 (3). In the same year, the association of NDM, CH, congenital glaucoma, hepatic fibrosis, and polycystic kidney disease

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were reported in two siblings with the hypothesis that it might constitute a new syndrome (4). *GLIS3* mutations (9p24.2, OMIM*610192) were first associated as the cause of the coexistence of persistent NDM and CH in six cases in 2006 (5).

GLIS3 encodes the zinc finger protein GLI-like protein 3 (*GLIS3*) (6). The protein is expressed early in embryogenesis and tissue expression plays a critical role in the development of pancreatic β cells, the thyroid gland, eyes, liver, and kidneys, and to a lesser extent heart, skeletal muscles, stomach, brain, lungs, adrenal glands, testes, ovaries, uterus, and bones (3,5,6). To date, only 22 patients with *GLIS3* variants variability have been reported and express significant phenotypic variability. The phenotypic features described so far include small for gestational age (SGA) infant, congenital glaucoma, polycystic kidney disease, cholestatic hepatic fibrosis, pancreatic exocrine insufficiency, developmental delay, dysmorphic facial features, sensorineural deafness, osteopenia, and skeletal anomalies (2,7,8).

Genetic evaluation was performed in a 17-year-old patient, who has been followed up in our clinic since infancy, because of the coexistence of permanent NDM, CH, glaucoma, developmental delay, and facial dysmorphism. A significant mutation was detected in the *GLIS3* gene. Since *GLIS3* mutations are a very rare cause of persistent neonatal syndromic diabetes, the case is presented to expand the published information about this rare condition.

Case Report

A forty-day-old male infant presented with complaints of feeding difficulties and fatigue. He was born at term by spontaneous vaginal delivery with a birth weight of 2800 g. The parents were first-degree cousins. In the follow-up after emergency intervention, high blood sugar (>200 mg/dL) and primary hypothyroidism [elevated thyroid stimulating hormone (TSH) and low free T4] were detected and insulin (0.4-0.6 IU/kg/day) and levothyroxine (10 mcg/kg/day) treatments were started. Glaucoma was detected during eye examination, triggered by the finding of corneal clouding. Hearing evaluation was normal. When the patient was four months old, the thyroid gland was found to be normal in size [+1.5 standard deviation (SD)] and *in situ* on ultrasound (USG). Serum thyroglobulin level was 707 ng/mL (3.5-77), urinary iodine level was 10 µg/dL (normal range 10-46). He was operated at the age of two years for unilateral undescended testis. At the age of 6 years and 10 months, his psychometric assessment was compatible with the age of 4.5-5 years. Brain magnetic resonance imaging (MRI) performed at the age of seven years was normal, and bone age was consistent with chronological age. Proteinuria was detected during diabetes follow-up at the age of eight. Abdominal USG evaluations at different periods were normal. There were no signs of hepatic fibrosis, cholestasis, or polycystic kidney disease. Thyroid stimulating hormone (TSH), free thyroxine (fT4), thyroid autoantibody levels, and anti-endomysium IgA concentration during follow-ups were normal. In the last seven years of follow-up, glycosylated hemoglobin levels were between 8.2-10.6%. Multiple dose subcutaneous insulin therapy with insulin detemir and insulin aspart continues at a dose of 1.1 u/kg/day. The most recent levothyroxine treatment dose was 175 mcg/day. Treatment and follow-up for glaucoma continues. The spot urine microalbumin/creatinine ratio in the follow-up of proteinuria has been <30 mg/g for the last year and he is followed without treatment. On the last physical examination, the 17-year-old patient's weight was 56.9 kg (-1.3 SD), height was 172.1 cm (-0.45 SD), and body mass index was 19.2 kg/m² (-1.3 SD). Pubertal assessment was consistent with Tanner stage 5. The patient had a long facial appearance, bilateral low-set ears, a long philtrum with a thin vermilion border of the upper lip, and multiple nevi smaller than 1 cm on the face and body (Figure 1). Dual-energy X-ray absorptiometry evaluation of patient to exclude osteopenia was normal and he had no history of fracture. His school performance was poor. In the last psychometric evaluation made with the Kent EGY test, the mental age was found to be 9.5 years, and the intelligence score was 69, while his chronological age was 17 years. Echocardiographic and repeated hearing examinations were normal. Genetic evaluation was performed in the patient due to the coexistence of permanent NDM, CH, congenital glaucoma, developmental delay, and facial dysmorphic findings. A homozygous exon 10-11 deletion of the *GLIS3* gene was detected. Furthermore, it was confirmed that both parents were heterozygous for this mutation. The genetic evaluation findings are thought to be compatible with the phenotypic characteristics of the patient.

Molecular Analysis

DNA isolation from the peripheral blood samples was performed using the MagNAPure LC DNA isolation kit (Roche Diagnostic GmbH, Mannheim, Germany) and the MagNAPure LC 2.0 (Roche Diagnostic Ltd., Rotkreuz, Switzerland) device according to the manufacturer's instructions. Quantification of DNA concentration and enriched library was performed with a Qubit® 3.0 Fluorometer (Invitrogen, Life Technologies Holdings Pte Ltd., Malaysia).

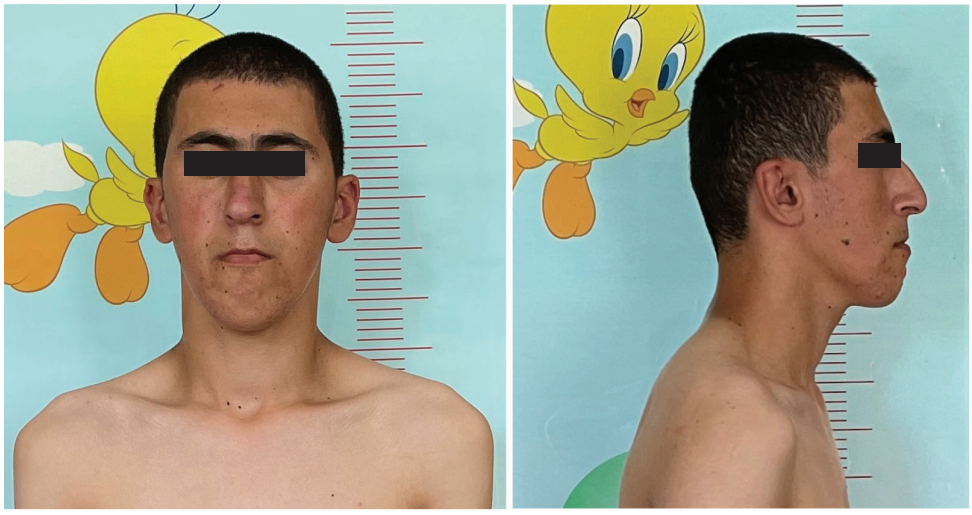

Figure 1. Facial dysmorphic findings in the patient

Table 1. Comparison of the phenotype and genotype characteristics of the presented patient with the previously reported Turkish patient and the other patient from the literature with the same mutation

	Previously reported Turkish patient	Previously reported patient with the same mutation	The presented patient
Sex	Male	Female	Male
Origin	Turkish	Yemeni	Turkish
Birth weight, g	1520	1235	2800
Gestation week	30	36	39
Age at diagnosis of ND	21 days	3 days	40 days
Hypothyroidism	+	+	+
Congenital glaucoma	-	+	+
Kidney disease	+	+	-
Exocrine pancreas insufficiency	-	+	-
Liver disease	+	+	-
Facial dysmorphism	+	+	+
Developmental delay	+	+	+
Age at death	6 months	NA	Alive (17 years)
Mutation type	Exons 3-4 del/exons 3-4 del	Exons 10-11 del/exons 10-11 del	Exons 10-11 del/exons 10-11 del

ND: neonatal diabetes, NA: not available

Library size distribution was measured with Agilent 2100 Bioanalyzer (Agilent Technologies, Waldbronn, Germany). Clinical Exome Solution kit (SOPHiA GENETICS, Saint-Sulpice, Switzerland) was used for library preparation and exome enrichment. The DNA sequencing was performed on Illumina NextSeq 500 instrument (Illumina, Inc., San Diego, CA, USA). Bioinformatic analysis was carried out via Sophia DDM version 5.10.8 (SOPHiA GENETICS, Saint Sulpice, Switzerland). Using dose analysis, this test may be able to detect copy number variation. In the presented patient a homozygous *GLIS3* exon 10 and 11 deletion was identified (NM_001042413.1). This deletion was also found to be heterozygous in both parents.

Discussion

NDM and CH syndrome are associated with mutations in the *GLIS3* gene (5). Most of the patients reported to date had ≥1 exon deletion in this gene (2,7,8). We present a case with coexisting NDM, CH, and congenital glaucoma and homozygous *GLIS3* exon 10-11 deletions. In the literature, the same deletion was described in a patient with NDM, CH, SGA, developmental delay, fibrotic liver cholestasis, polycystic kidney disease, and pancreatic exocrine insufficiency (Table 1). During the presented patient's 17-year follow-up, no symptoms of polycystic kidney disease, hepatic fibrosis, cholestasis, or exocrine pancreatic

insufficiency occurred. Furthermore, less common clinical findings of the condition, such as deafness, osteopenia, bone fractures, skeletal dysplasia, hernia, and cardiac illness, were not present in this case (7,8). Most of the previously described patients had a history of SGA or preterm birth (2,7,8). Although the presented patient had a history of normal delivery at term, birth weight was at the lower limit of normal. The association of hypospadias and bilateral undescended testis was reported in only one case previously, and coincidence was considered because extensive genetic evaluation was not performed (9). In the presented case, there was unilateral undescended testis but no hypospadias. Unlike the previously reported patients, the presented patient had many nevi over his body, all of which were less than 1 cm in diameter (7,8).

The present case is one of the oldest living patients described with a *GLIS3* variant as he has reached young adulthood. Interestingly, the presented case and the two other oldest reported patients had no liver, exocrine pancreas abnormalities, or kidney disease (2,5,7). We hypothesize that the absence of parenchymatous organ disease allows these patients to reach early adulthood. Of the other two older patients, the French patient who lived to adulthood and had a homozygous 149kb del and did not have congenital glaucoma (5) while in the other oldest patient, with p.Arg589Trp/exons 1-11 del, neonatal diabetes was not accompanied by CH, congenital glaucoma, or facial dysmorphism (7).

Although fT4 was within the normal range with treatment, TSH elevation, fluctuation, and TSH resistance, as well as thyroid agenesis and hypoplasia were frequently reported conditions (2,8). The thyroid gland of the presented patient was of normal size and in its normal location. Although fT4 and TSH were within normal limits during follow-up, levothyroxine treatment was maintained at > 3 mcg/kg/day (> 100 mcg/m²/day), indicating TSH resistance. Elevated serum thyroglobulin, which was reported in previously described cases, was also present in our patient (8,9).

The presented case is the second Turkish patient reported with a *GLIS3* variant. The previously reported Turkish patient had facial dysmorphism, developmental delay, and liver and kidney disease, but he did not have SGA, congenital glaucoma, exocrine pancreatic insufficiency, or skeletal disease (Table 1). In that case exon 3-4 deletions were detected, and the child died at the age of six months (7,9).

Conclusion

We present a case with homozygous exon 10-11 deletion in the *GLIS3* gene to contribute to the genotypic and phenotypic characterization of patients with neonatal diabetes and CH syndrome, a rare cause of neonatal diabetes. Furthermore, the identification of other accompanying clinical features in these cases will aid understanding of the disorder, and facilitate early diagnosis and appropriate treatment of patients with this condition.

Ethics

Informed Consent: Consent form was filled out by a participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Emre Sarıkaya, Mustafa Kendirci, Concept: Emre Sarıkaya, Mustafa Kendirci, Munis Dündar, Design: Emre Sarıkaya, Mustafa Kendirci, Mikail Demir, Data Collection or Processing: Emre Sarıkaya, Mikail Demir, Analysis or Interpretation: Emre Sarıkaya, Mikail Demir, Munis Dündar, Literature Search: Emre Sarıkaya, Writing: Emre Sarıkaya, Mustafa Kendirci, Mikail Demir.

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References

1. Grulich-Henn J, Wagner V, Thon A, Schober E, Marg W, Kapellen TM, Haberland H, Raile K, Ellard S, Flanagan SE, Hattersley AT, Holl RW. Entities and frequency of neonatal diabetes: data from the diabetes documentation and quality management system (DPV). Diabet Med 2010;27:709-712.
2. London S, De Franco E, Elias-Assad G, Barhoum MN, Felszer C, Paniakov M, Weiner SA, Tenenbaum-Rakover Y. Case Report: Neonatal Diabetes Mellitus Caused by a Novel GLIS3 Mutation in Twins. Front Endocrinol (Lausanne) 2021;12:673755.
3. Kim YS, Nakanishi G, Lewandoski M, Jetten AM. GLIS3, a novel member of the GLIS subfamily of Krüppel-like zinc finger proteins with repressor and activation functions. Nucleic Acids Res 2003;31:5513-5525.
4. Taha D, Barbar M, Kanaan H, Williamson Balfe J. Neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, polycystic kidneys, and congenital glaucoma: a new autosomal recessive syndrome? Am J Med Genet A 2003;122:269-273.
5. Senée V, Chelala C, Duchatelet S, Feng D, Blanc H, Cossec JC, Charon C, Nicolino M, Boileau P, Cavener DR, Bougnères P, Taha D, Julier C. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. Nat Genet 2006;38:682-687. Epub 2006 May 21

6. Beak JY, Kang HS, Kim YS, Jetten AM. Functional analysis of the zinc finger and activation domains of Glis3 and mutant Glis3(NDH1). Nucleic Acids Res 2008;36:1690-1702. Epub 2008 Feb 7
7. Dimitri P, Habeb AM, Gurbuz F, Millward A, Wallis S, Moussa K, Akcay T, Taha D, Hogue J, Slavotinek A, Wales JK, Shetty A, Hawkes D, Hattersley AT, Ellard S, De Franco E. Expanding the Clinical Spectrum Associated With GLIS3 Mutations. J Clin Endocrinol Metab 2015;100:1362-1369. Epub 2015 Aug 10
8. Splittstoesser V, Vollbach H, Plamper M, Garbe W, De Franco E, Houghton JAL, Dueker G, Ganschow R, Gohlke B, Schreiner F. Case Report: Extended Clinical Spectrum of the Neonatal Diabetes With Congenital Hypothyroidism Syndrome. Front Endocrinol (Lausanne). 2021;12:665336.
9. Dimitri P, De Franco E, Habeb AM, Gurbuz F, Moussa K, Taha D, Wales JK, Hogue J, Slavotinek A, Shetty A, Balasubramanian M. An emerging, recognizable facial phenotype in association with mutations in GLI-similar 3 (GLIS3). Am J Med Genet A 2016;170:1918-1923. Epub 2016 May 5