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Case report

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

Sarıkaya E et al. 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 (SGA) 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 case 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 syndrome (NDH) is a rare condition caused by homozygous or compound heterozygous mutations in the GLIS3 gene. Small for gestational age (SGA), 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 22 cases described so far. We present a male case with neonatal diabetes, congenital hypothyroidism, congenital glaucoma, developmental delay, and facial dysmorphic features. 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 congenital hypothyroidism 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 6 months of life. Although it is reported to be 1 in 90,000-300,000 in different studies, it is estimated that it may be at least 3-10 times more common in the Middle East Region, where consanguineous marriage is high (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 were reported in two siblings with the thought that it might be a new syndrome (4). GLIS3 mutations (9p24.2, OMIM*610192) were first associated in 2006 as the cause of the coexistence of persistent NDM and CH in six cases (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, thyroid glands, 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, 22 patients with significant phenotypic variability have been reported. 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 are the phenotypic features described so far (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 dysmorphic features. 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 its clinical features.

Case Report
A forty-day-old male infant was presented with complaints of feeding difficulties and fatigue. It was learned that he was born at term with a spontaneous vaginal delivery of 2800 g and the parents were first-degree cousins. In the follow-up after the emergency intervention, high blood sugar and primary hypothyroidism were detected, thereafter insulin and levothyroxine treatments were started. Glaucia was detected during the eye examination because 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 SD) and in situ in the evaluation made with ultrasound (USG). Serum thyroglobulin level was 707 ng/mL (3.5-77), urinary iodine level was 10 µg/dL. He was operated at the age of two years for unilateral undescended testes. At the age of 6 years and 10 months, his psychometric assessment was compatible with the age of 4.5-5.5 years. Brain magnetic resonance imaging (MRI) performed at the age of seven years was normal, and bone age was consistent with chronologic 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-thyroid peroxidase IgA concentration during follow-ups were normal. In the last 7 years of follow-up, glycocalcified globulin (HbA1C) 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. Levothyroxine treatment continues at a dose of 175 mcg/day lastly. 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 one year and followed without treatment. At 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 (BMI) 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 (DXA) evaluation of patient to exclude osteopenia was normal, who 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. 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. It was thought that the result of the genetic evaluation was 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). 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. As a consequence of our patient's molecular study, homozygous GLIS3 exon 10 and 11 homozygous deletions were 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 so far had ≥1 exon deletion in this gene (2, 7, 8). We present a case with NDM, CH, and congenital glaucoma coexistence and homozygous 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 our patient’s 17-year follow-up, no symptoms of polycystic kidney disease, hepatic fibrosis, or exocrine pancreatic insufficiency occurred. Furthermore, less common clinical findings of the disease such as deafness, osteopenia, bone fractures, skeletal dysplasia, hernia, and cardiac illness were not present in our case (7, 8). Most of the previously described patients had a history of SGA or preterm birth (2, 7, 8). Although our case had a history of normal delivery at term, birth weight was at the lower limit of normal. The association of hypospadias and bilateral undescended testes was reported in only one case previously, and coincidence was considered because extensive genetic evaluation was not performed (9). In our case, there was unilateral undescended testis. Unlike the reported patients, he had many nevi in his body, which were less than 1 cm in diameter (7, 8). Our case is one of the oldest living patient, who has reached young adulthood. Our patient and the two other oldest reported patients had no liver, exocrine pancreas, or kidney disease (2, 5, 7). We think that the absence of parenchymatous organ disease allows these patients to reach early adulthood. In contrast to our case, the French patient who lived to adulthood and had homozygous 149kb del did not have congenital glaucoma (5). In the other oldest patient with p.Arg589Trp/exons 1–11 del, neonatal diabetes was not accompanied by congenital hypothyroidism, 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 patient was of normal size and in its normal location. Although fT4 and TSH were within normal limits during our case's follow-up, levothyroxine treatment was maintained at >3mcg/kg/day (>100mcg/m²/day), indicating TSH resistance. The elevation of thyroglobulin, which was also reported in previously described cases, was also present in our patient (8, 9).

Our case is the second Turkish patient reported. The previously reported Turkish patient had facial dysmorphism, developmental delay, liver, and kidney diseases, but he did not have SGA, congenital glaucoma, exocrine pancreatic insufficiency, and skeletal disease (Table 1). Exon 3-4 deletions had been detected in that case, which had died at the age of 6 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 congenital hypothyroidism syndrome, which is a rare cause of neonatal
Furthermore, the identification of other accompanying clinical features in the cases will aid to better understand the disorder, and early diagnosis and appropriate treatment of the patients.

References

Figure 1. Facial dysmorphic findings of the patient
Table 1. Comparison of the phenotype and genotype characteristics of our patient with the previously reported Turkish patient and the patient with the same mutation

<table>
<thead>
<tr>
<th></th>
<th>Previously reported Turkish patient</th>
<th>Previously reported patient with the same mutation</th>
<th>Our patient</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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<td>Male</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
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<td>Turkish</td>
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<td><strong>Birth weight, g</strong></td>
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<td>1235</td>
<td>2800</td>
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<td><strong>Gestation week</strong></td>
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<tr>
<td><strong>Age at diagnosis of ND</strong></td>
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<td>40 days</td>
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<tr>
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<td>+</td>
<td>+</td>
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<td>+</td>
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<td>-</td>
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<td>-</td>
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<tr>
<td><strong>Liver disease</strong></td>
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<td>-</td>
</tr>
<tr>
<td><strong>Facial dysmorphism</strong></td>
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<td>Exons 10-11 del/ exons 10-11 del</td>
<td>Exons 10-11 del/ exons 10-11 del</td>
</tr>
</tbody>
</table>

ND: Neonatal diabetes, NA: Not available.