A Case of Late-Onset Monogenic Diabetes Due to a Homozygous Variant in the GCK Gene

Berna Eroğlu Filibeli1, Gönül Çatlı2, İlkay Ayrancı1, Hayrullah Manyas1, Özgür Kırbıyık3, Bumin Dündar2

1Tepecik Training and Research Hospital, Department of Pediatric Endocrinology, Izmir, Turkey
2Katip Celebi University, Department of Pediatric Endocrinology, Izmir, Turkey
3Tepecik Training and Research Hospital, Department of Genetics, Izmir, Turkey

Background-Aim

In Glucokinase (GCK) gene,

- Heterozygous loss-of-function mutations cause MODY type 2, characterized by asymptomatic fasting hyperglycemia.
- Homozygous loss-of-function mutations give rise to permanent neonatal diabetes mellitus (DM).

Previously, only two cases diagnosed with DM in adolescence and had homozygous GCK mutations were reported.

- Variants in these patients have been shown to exhibit inactivated kinetics that are indistinguishable from neonatal onset mutations, but exhibit thermostability properties, which alleviate disease severity.

- **Aim:** To present genotypic and phenotypic features of a patient diagnosed with DM at the age of 3 years due to a homozygous variant in the GCK gene.

Case

13 years old, boy

- He was diagnosed with DM at the age of three years with polyuria, polydipsia
- Insulin glargine (0.2U/kg/day) was adequate for good glycemic control
- HbA1c values in the previous year were between 6-7%
- No ketoacidosis during follow-up

**Medical history:** Term, 2500 g birth weight

**Family history:** His parents were first degree cousins and numerous relatives with DM were present in the family (Figure 1).

**Physical examination**

- Weight +0.18 SDS
- Height +0.74 SDS
- Puberty Tanner stage II
- Other system examinations normal

**Laboratory (At diagnosis)**

- Fasting serum glucose: 172 mg/dL (N, 60-100)
- C-peptide: 1.1 ng/mL (N, 0.9-7.1)
- Insulin <2 mIU/mL (N, 1.9-23)
- HbA1c: 7% (N, 4-6%)
- Anti-glutamic acid decarboxylase: Negative
- Anti insulin antibody: Negative

**Figure 1. Pedigree**

**MODY panel (GCK, HNF1A, HNF1B and HNF4A genes)**

**Proband**

**Mother**

**Father**

**In GCK gene, c.1222 G>T novel homozygous variant**

- His mother and father were heterozygous for the same variant
- Mother’s fasting serum glucose 108 mg/dL, HbA1c 6.2%
- Father’s fasting serum glucose 130 mg/dL, HbA1c 6.2%

**Conclusion**

- In GCK mutations, the homozygous and heterozygous status of the variant, as well as protein instability and thermostability properties may also contribute to the genotype-phenotype correlation.
- Despite the homozygous mutation in our patient, he had late-onset and mild disease, which may be related to the thermostability of GCK protein.
- Molecular genetic analysis of MODY genes in patients, whose clinical and laboratory findings do not match with type 1 DM can define novel mutations and provide a better understanding of the genotype-phenotype correlation in MODY.