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

Berna Eroğlu Filibeli[1], Gönül Çatlı[2], İlkay Ayrancı[1], Hayrullah Manyas[1], Özgür Kırbıyık[3], Bumin Dündar[2]

[1]*Tepecik Training and Research Hospital, Department of Pediatric Endocrinology, Izmir, Turkey*
[2]*Katip Celebi University, Department of Pediatric Endocrinology, Izmir, Turkey*
[3]*Tepecik 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
- Insülin glargine (0.2U/kg/day) was addequate 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).

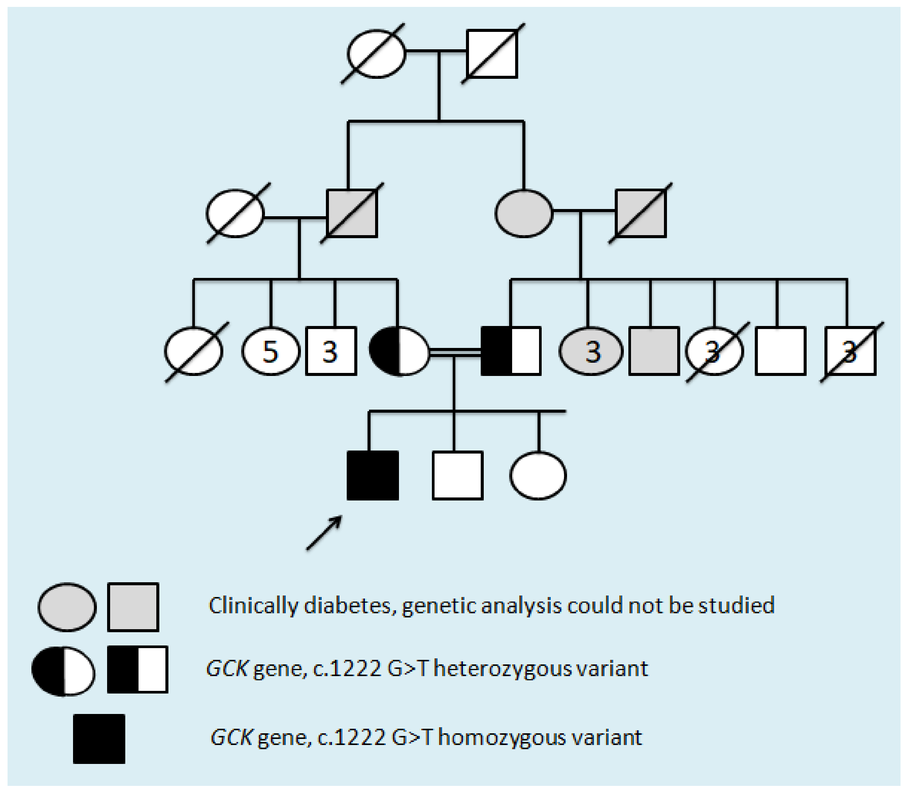


Figure 1. Pedigree

Physical examination

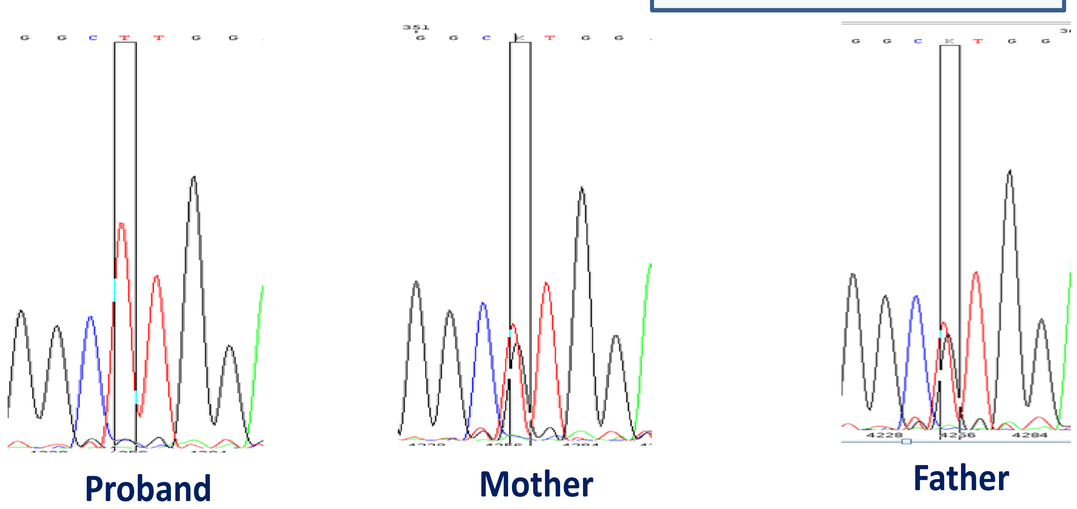
- Weight +0,18 SDS
- Height +0,74 SDS
- Puberty Tanner stage II
- Other system examinations normal

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

- Negative diabetes autoantibodies
- Low insulin requirement
- No ketoacidosis
- Family history for DM

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



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.