*JCEM Case Reports*, 2024, **2**, luae226
https://doi.org/10.1210/jcemcr/luae226
Advance access publication 4 December 2024
**Case Report**

# Mild Congenital Hyperinsulinism Caused by Mutation in Human *Glucokinase* Gene

**Leila Salikhovna Sozaeva,[1,*] Sabina Kalandarovna Ismailova,[1,*] Irina Yurievna Chernyak,[2] Sergey Vladimirovich Popov,[1] Victoriya Vitalievna Zakharova,[1] and Igor Sergeevich Chugunov[1]**

[1]Endocrinology Research Centre, Moscow, 117036, Russian Federation
[2]Children's Regional Clinical Hospital, Krasnodar, 350007, Russian Federation

**Correspondence**: Leila Salikhovna Sozaeva, MD, PhD, Endocrinology Research Centre, Dmitriya Ulyanova Street, 11/2, Moscow, 117036, Russian Federation. Email: Leila.sozaeva@gmail.com.
*Co-first author.

## Abstract

Congenital hyperinsulinism (CHI) is a rare hereditary disease characterized by the development of hypoglycemia in both infants and adult patients. CHI may be induced by activating mutations in the *glucokinase* (*GCK*) gene, which encodes the human glucokinase enzyme. This form of the disease is characterized by considerable phenotypic heterogeneity and may vary in severity of its course. We present a familial case report of mild CHI caused by a novel variant, c.212T > C (p.Val71Ala), in the *GCK* gene in a 41-year-old mother and a 15-year-old daughter. The clinical picture of hypoglycemia in the patients was not pronounced, which makes this clinical case remarkable. Moreover, a variant of uncertain clinical significance, c.1903G > A (p.Ala635Thr), in the *ABCC8* gene was detected, which may also have contributed to the course of the disease in these patients.

**Key Words:** congenital hyperinsulinism, hyperinsulinemic hypoglycemia, glucokinase, *GCK* gene

## Introduction

Congenital hyperinsulinism (CHI) is a rare disease characterized by dysregulated insulin secretion leading to hypoglycemia. CHI is the most common cause of persistent hypoglycemia in neonates and infants. There are 16 various genes known to be responsible for CHI development: *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *UCP2*, *HNF4A*, *HNF1A*, *HK1*, *KCNQ1*, *CACNA1D*, *FOXA2*, *EIF2S3*, *PGM1*, and *PMM2*. The proteins encoded by these genes are involved in regulating insulin secretion by the pancreatic β-cells. CHI can also be associated with genetic syndromes and can be secondary to intrauterine growth restriction, maternal diabetes, birth asphyxia, etc. [1].

One of the proteins involved in the regulation of carbohydrate metabolism is glucokinase, an enzyme encoded by the *GCK* gene. The *GCK* gene consists of 12 exons and is predominantly expressed in pancreatic β-cells but also in liver cells and brain neurons. Glucokinase phosphorylates glucose to glucose-6-phosphate, serving as a substrate for the glycolytic pathway, which triggers adenosine triphosphate (ATP) generation and glucose-dependent insulin secretion [2].

The *GCK* gene pathogenic variants may be involved in the pathogenesis of both hyper- and hypoglycemia. Inactivating variants in the *GCK* gene cause maturity-onset diabetes of the young type II, while activating variants in the *GCK* gene induce CHI development [3]. Hypoglycemia caused by activating mutations develops due to a glucokinase equilibrium shifting to a form with higher glucose affinity and a lower threshold for glucose-stimulated insulin secretion [4].

Clinical manifestations of activating mutations in the *GCK* gene may widely vary from severe neonatal hypoglycemia with seizures and delayed psychomotor development to asymptomatic hyperinsulinemic hypoglycemia detected in adulthood [5].

More than 20 various pathogenic variants in the *GCK* gene causing CHI are described in the literature [5]. The variants predominantly affect an allosteric binding site, which is responsible for the shift from an active glucokinase form to its inactive form. Most patients with activating *GCK* mutations have a persistent hypoglycemia with late-onset disease. However, severe pharmacoresistant clinical cases with neonatal manifestation were also reported [6–10].

## Case Presentation

Patient Z. (proband), a 15-year-old female, presented to the endocrinologist for recurrent hypoglycemia episodes that started when she was 14.

According to the family history, the proband was born with a birth weight of 2980 g and length of 50 cm. The Apgar score was 8 to 9 points. It was the third pregnancy for the patient's other and the second spontaneous vaginal delivery. The pregnancy was complicated by hypertension. No history of developmental psychomotor disturbances or other anomalies were

**Received:** 13 July 2024. **Editorial Decision:** 19 November 2024. **Corrected and Typeset:** 4 December 2024

detected in the patient's neonatal period. No information on previous blood glucose tests was found in her medical records.

Hypoglycemia [1.87 mmol/L, 33.7 mg/dL (reference range: 3.3-5.5 mmol/L, 70-140 mg/dL)] was first documented in July 2022 at the age of 13 years when the proband lost consciousness. Blood glucose levels were measured by the ambulance team using a glucometer after the patient regained consciousness. No seizures, excessive sweating, or significant tachycardia before, during, or after loss of consciousness are recalled by the proband or her mother. After that, the patient has not been examined for 1 year. She had no complaints, her general condition was satisfactory, and no blood glucose tests were performed.

At the patient's age of 14 years, hypoglycemia was again detected by routine laboratory tests for community-acquired pneumonia.

## Diagnostic Assessment

The patient was referred to an endocrinologist for further examination. The test results revealed hyperinsulinemic hypoglycemia. The patient was further referred to the Endocrinology Research Centre in Moscow, Russia, where the diagnosis was confirmed (Table 1). Iatrogenic hypoglycemia caused by insulin administration was ruled out by C-peptide levels, which were also elevated. No traces of sulfonylureas were found in the patient's blood sample. Thus, this group of drugs was also excluded as a possible trigger for the development of hypoglycemia. The age of symptom onset and excessive insulin release during hypoglycemia episodes were suggestive of insulinoma, but endoscopic ultrasound, computed tomography, and magnetic resonance imaging of the abdominal cavity failed to localize any signs of mass lesion in the pancreas. Insulin autoimmune syndrome was excluded based on insulin antibody levels. The patient's glycemic profile was quite remarkable: persistent asymptomatic hypoglycemia with progressively dropping glucose levels immediately after ingestion of fast carbohydrates, while with a normal diet based on complex carbohydrates, fats, and proteins, glucose levels were stable and remained in the range of 2.8 to 3.2 mmol/L, 50.4 to 57.6 mg/dL (reference range: 3.3-5.5 mmol/L, 70-140 mg/dL).

Blood glucose levels in the proband's father were normal; the proband's mother had hypoglycemia of 3.0 mmol/L, 54 mg/dL (reference range: 3.3-5.5 mmol/L, 70-140 mg/dL). Given the uncommon glycemic profile, asymptomatic hypoglycemia in the proband's mother, and no evidence of an insulinoma in the proband's pancreas, the presence of activating mutations in the patient's *GCK* gene was suggested. A molecular diagnostics detected a novel heterozygous mutation, c.212T > C (p.Val71Ala), in exon 3 of the *GCK* gene. The variant is located in a moderately conserved position, and computational algorithms predict its pathogenic effect on the protein. Molecular testing of the *GCK* gene in the proband's mother revealed an identical heterozygous mutation. This mutation was previously detected in a child with CHI and presented at the 7th ESE Young Endocrinologists and Scientists meeting as an abstract [11], but it has not yet been described in an article. Given that the pathogenic variant was previously identified and that we detected it in both the proband and her mother, and based on pathogenicity prediction algorithm data, it is reasonable to assume that the probability of this pathogenic variant being pathogenic is high. Functional studies of this gene variant have not been performed. The proband's maternal grandmother's blood glucose levels were within a normal range. The maternal grandfather died of myocardial infarction; no data on his blood glucose levels are available, so it cannot be clarified whether this variant was inherited by the proband's mother from her parents or whether it occurred de novo.

We also detected an additional variant, c.1903G > A (p.Ala635Thr), in exon 13 of the *ABCC8* gene. The variant is registered in the Genome Aggregation Database v4.0.0 as a heterozygous mutation with a frequency of 0.001113%. It is located in a nonconserved position, and the algorithm-predicted effect of this variant on the protein is neutral; therefore, the clinical significance of this variant has not been assessed.

The sequence was deposed to the NCBI Sequence Read Archive with Bioproject accession number PRJNA1168410. The next-generation sequencing data are available at biosample SAMN44240844. The Sanger sequence of the *ABCC8* gene is available with accessions SRX26345179, SRX26345178. The Sanger sequence of the *GCK* gene is available with accessions SRX26345177, SRX26345176, SRX26344922, SRX26344921.

**Table 1. The blood test results of patient Z**

| Parameter | Result | Reference values |
|---|---|---|
| Glycated hemoglobin (%) | 3.4 | 4-6 |
| Glucose (blood serum) | 1.94 mmol/L (34.9 mg/dL) | 3.3-6.1 mmol/L (59.5-109.9 mg/dL) |
| Insulin | 30.29 μU/mL (210.35 pmol/L) | 2.6-24.9 μU/mL (18-172.9 pmol/L) |
| C-peptide | 4.81 ng/mL (1.5 nmol/L) | 1.1-4.4 ng/mL (0.36-1.46 nmol/L) |
| Anti-insulin antibodies | 2.54 U/mL | 0-10 |

## Treatment

The patient and her mother were recommended to regularly measure blood glucose levels by glucometer and to follow a diet based on complex carbohydrates with restriction of fast carbohydrates.

## Outcome and Follow-up

The diet resulted in stabilization of the glucose levels in the patient's mother. The patient complied with the recommendations as well, albeit with recurrent laboratory, not symptomatic, signs of hypoglycemia. In case of persistent symptomatic hypoglycemia, the administration of diazoxide will be considered in the future.

## Discussion

The clinical picture of CHI may vary in severity and may depend on a variant in the *GCK* gene. Most cases are characterized by mild hypoglycemia, but some pathogenic variants result in severe symptomatic hypoglycemia [3]. Patients with pathogenic variants in the *GCK* gene usually respond to diazoxide therapy, but in some cases hypoglycemia requires no intervention [5].

Challis et al published a familial case report of CHI in adult patients due to an activating mutation in the *GCK* gene [12]. A

heterozygous activating mutation, p.Val389Leu, in the *GCK* gene was found in the 63-year-old female patient (proband) and her family members. The hypoglycemia was detected by a routine blood glucose test. A diagnosis of hyperinsulinemic hypoglycemia was confirmed. The proband's blood glucose levels remained between 2.1 mmol/L (37.8 mg/dL) and 2.9 mmol/L (52 mg/dL) throughout 34 hours of fasting (reference range: 3.3-5.5 mmol/L, 70-140 mg/dL), while an extended oral glucose tolerance test revealed a progressive glucose level decrease started at 30 minutes down to minimum values [< 2.0 mmol/L, 36 mg/dL at 180 minutes(reference range: 3.3-5.5 mmol/L, 70-140 mg/dL)]. The proband was intolerant of acarbose and diazoxide and showed no response to subcutaneous administration of octreotide or to oral administration of nifedipine. The recommendation was to follow a low glycemic index diet. The proband's father presented at the age of 77 with a history suggestive of hypoglycemia. He received diazoxide therapy with subjective symptomatic improvement despite evidence of persisting chronic hypoglycemia. Hyperinsulinemic hypoglycemia was also diagnosed in the proband's son, brother, and niece. In these patients, an extended oral glucose tolerance test revealed a progressive glucose level decrease as well. None of them received medications, but they followed a low glycemic index diet. In our proband and her mother, no extended oral glucose tolerance test was performed, but the attempts to prevent glucose levels from dropping below 3 mmol/L by fast carbohydrate food ingestion or by glucose 10% IV infusion resulted in an even more pronounced decrease in glucose levels below 2 mmol/L (36 mg/dL). Of note, our proband had no clinical manifestations of hypoglycemia even with a glucose level decrease down to 1.8 mmol/L (32 mg/dL) (reference range: 3.3-5.5 mmol/L, 70-140 mg/dL).

In the literature, there are also case reports of severe hyperinsulinism requiring pancreatectomy. Li et al presented 10 phenotypically heterogeneous clinical cases of CHI caused by glucokinase dysfunction. Four of 10 patients had severe hypoglycemia without any response to diazoxide therapy and subsequently underwent pancreatectomy. Two of these 4 patients required additional therapy due to persistent and severe hypoglycemia [13].

The CHI clinical picture may also vary within the same family. Beer et al presented a familial case of CHI caused by a pathogenic variant in the *GCK* gene [10]. The proband had postnatal records of hypoglycemia with seizure onset at 2 years, and at 3.6 years hyperinsulinemic hypoglycemia was diagnosed. Following the diagnosis, the proband was treated with diazoxide. The proband's father complained of feeling lightheaded and weak with prolonged intervals between food ingestions. He was diagnosed with moderate hypoglycemia and required no therapy.

Thus, the severity of CHI caused by pathogenic variants in the *GCK* gene can range from mild or moderate, when the symptoms can be relieved by a low glycemic index diet or diazoxide therapy, to severe, sometimes requiring pancreatectomy [8, 14, 15].

In our familial case, another novel variant was detected in the *ABCC8* gene. Pathogenic variants in this gene may lead to both diabetes mellitus and hypoglycemic syndrome. The *ABCC8* gene located on chromosome 11p15. 1 encodes the SUR-1 receptor to sulphonylureas on an ATP-sensitive potassium channel (KATP channel) in pancreatic β-cells. The KATP channel regulates the potassium influx and efflux into cells. An increase in ATP/adenosine diphosphate ratio causes depolarization of the cell membrane inducing KATP channel closure and activation of voltage-dependent calcium channels, leading to calcium influx and the release of insulin. Inactivating mutations in the *ABCC8* gene cause dysfunction in KATP channels, resulting in sustained membrane depolarization independent of blood glucose levels, leading to hyperinsulinism [16, 17]. Prognosis in such forms of CHI may vary widely from the development of irreversible central nervous system lesions and the need for lifelong treatment to cases that require no intervention, which is determined both by the mechanism of inheritance and the pathogenic variant itself [18]. In the presented clinical case, the variant in the *ABCD8* gene was not described previously, and its pathogenicity is doubtful. Further functional studies are necessary to investigate the impact of this variant on the course of the disease.

The CHI forms associated with glucokinase dysfunction are rather rare. A number of clinical cases demonstrating phenotypic heterogeneity of the disease associated with activating mutations in the *GCK* gene are described in the literature. We present a clinical case report of CHI, diagnosed de novo in 2 members of 1 family aged 15 years and 41 years without any history of clinical manifestations suggestive of hypoglycemia. In addition to a possibly pathogenic variant in the *GCK* gene, we also detected a variant of uncertain clinical significance in our patients' *ABCC8* gene. This clinical case demonstrates that CHI should be included in the differential diagnosis list for patients with hyperinsulinemic hypoglycemia detected in adulthood or adolescence, even if no episodes of hypoglycemia were recorded in their early life.

## Learning Points

- The clinical picture of CHI due to a pathogenic variant in the *GCK* gene has a heterogenicity ranging from mild asymptomatic forms to severe neonatal hypoglycemia.
- CHI due to a pathogenic variant in the *GCK* gene should be in the list of differential diagnoses for hyperinsulinemic hypoglycemia in adults and adolescents.
- Genetic verification of CHI is important for the choice of treatment of the patient and genetic counseling of the family.

## Contributors

All authors made individual contributions to authorship. L.S.S., S.K.I., I.Y.C., and I.S.C. were involved in the diagnosis and management of the patient. L.S.S., S.K.I., S.V.P., and V.V.Z. drafted the main manuscript. V.V.Z. performed the genetic tests. S.V.P. and I.S.C. supervised and reviewed the final draft. All authors reviewed and approved the final draft.

## Funding

The study was funded by the Ministry of Science and Higher Education of the Russian Federation (Grant Number: 075-15-2022-310).

## Disclosures

None declared.

## Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient's relatives or guardians.

## Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

## References


1. Giri D, Hawton K, Senniappan S. Congenital hyperinsulinism: recent updates on molecular mechanisms, diagnosis and management. *J Pediatr Endocrinol Metab*. 2021;0(0):000010151 520210369.
2. Iynedjian PB, Pilot PR, Nouspikel T, *et al*. Differential expression and regulation of the glucokinase gene in liver and islets of Langerhans. *Proc Natl Acad Sci U S A*. 1989;86(20):7838-7842.
3. Osbak KK, Colclough K, Saint-Martin C, *et al*. Update on mutations in glucokinase (*GCK*), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. *Hum Mutat*. 2009;30(11):1512-1526.
4. Ralph EC, Thomson J, Almaden J, Sun S. Glucose modulation of glucokinase activation by small molecules. *Biochemistry*. 2008;47(17):5028-5036.
5. Martínez R, Gutierrez-Nogués Á, Fernández-Ramos C, *et al*. Heterogeneity in phenotype of hyperinsulinism caused by activating glucokinase mutations: a novel mutation and its functional characterization. *Clin Endocrinol (Oxf)*. 2017;86(6):778-783.
6. Cuesta-Muñoz AL, Huopio H, Otonkoski T, *et al*. Severe persistent hyperinsulinemic hypoglycemia due to a De Novo glucokinase mutation. *Diabetes*. 2004;53(8):2164-2168.
7. Christesen HBT, Jacobsen BB, Odili S, *et al*. The second activating glucokinase mutation (A456V). *Diabetes*. 2002;51(4):1240-1246.
8. Gloyn AL, Noordam K, Willemsen MAAP, *et al*. Insights into the biochemical and genetic basis of glucokinase activation from naturally occurring hypoglycemia mutations. *Diabetes*. 2003;52(9): 2433-2440.
9. Barbetti F, Cobo-Vuilleumier N, Dionisi-Vici C, *et al*. Opposite clinical phenotypes of glucokinase disease: description of a novel activating mutation and contiguous inactivating mutations in human glucokinase (*GCK*) gene. *Mol Endocrinol*. 2009;23(12): 1983-1989.
10. Beer NL, Van De Bunt M, Colclough K, *et al*. Discovery of a novel site regulating glucokinase activity following characterization of a new mutation causing hyperinsulinemic hypoglycemia in humans. *J Biol Chem*. 2011;286(21):19118-19126.
11. Skarakis NS, Kanaka-Gantenbein C, Dimopoulou D, Sertedaki A, Karachaliou F. Congenital hyperinsulinism due to a novel activating glucokinase mutation: a case report and literature review. *Endocrine*. 2019;67:GP40. Doi:10.1530/endoabs.67.GP40
12. Challis BG, Harris J, Sleigh A, *et al*. Familial adult onset hyperinsulinism due to an activating glucokinase mutation: implications for pharmacological glucokinase activation. *Clin Endocrinol (Oxf)*. 2014;81(6):855-861.
13. Li C, Juliana CA, Yuan Y, *et al*. Phenotypic characterization of congenital hyperinsulinism due to novel activating glucokinase mutations. *Diabetes*. 2023;72(12):1809-1819.
14. Wabitsch M, Lahr G, Van De Bunt M, *et al*. Heterogeneity in disease severity in a family with a novel G68V *GCK* activating mutation causing persistent hyperinsulinaemic hypoglycaemia of infancy. *Diabet Med*. 2007;24(12):1393-1399.
15. Sayed S, Langdon DR, Odili S, *et al*. Extremes of clinical and enzymatic phenotypes in children with hyperinsulinism caused by glucokinase activating mutations. *Diabetes*. 2009;58(6): 1419-1427.
16. De Franco E, Saint-Martin C, Brusgaard K, *et al*. Update of variants identified in the pancreatic β-cell $K_{ATP}$ channel genes *KCNJ11* and *ABCC8* in individuals with congenital hyperinsulinism and diabetes. *Hum Mutat*. 2020;41(5):884-905.
17. Stanley CA. Perspective on the genetics and diagnosis of congenital hyperinsulinism disorders. *J Clin Endocrinol Metab*. 2016;101(3): 815-826.
18. Banerjee I, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Dunne MJ. Therapies and outcomes of congenital hyperinsulinism-induced hypoglycaemia. *Diabet Med*. 2019;36(1):9-21.