Heliyon 10 (2024) e35112

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Chinese carrier of the *HNF1A* p.Gln444fs variant exhibits enhanced response to sulfonylureas

Xiufang Wang [a,1], Wenzhuo Cheng [b], Zhongjing Wang [c], Chao Liu [d], Aiping Deng [e,**], Juyi Li [e,*,1]

[a] *Department of Pain, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[b] *Department of Pediatric, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Hubei, China*
[c] *Department of Endocrinology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[d] *Hubei Key Laboratory of Diabetes and Angiopathy, Hubei University of Science and Technology, Xianning, Hubei, China*
[e] *Department of Pharmacy, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*

ARTICLE INFO

Keywords:
HNF1A
MODY3
Monogenic diabetes
Precision therapy
Whole-exome sequencing

ABSTRACT

Background: We assessed the response to sulfonylureas and the functional characteristics of *HNF1A* mutations in patients with maturity-onset diabetes of the young type 3 (MODY3).
Methods: We recruited a family with suspected MODY in this study, and gene sequencing (whole-exome sequencing) was used to screen germline mutations. Luciferase reporter assays were used to evaluate the activity of the mutated genes.
Results: Heterozygous *HNF1A* variant (NM_000545.8:c.1330_1331del, p.Gln444fs) was identified in the proband and was not found in his father, grandmother, and nonrelated healthy controls. The mutant protein had 552 amino acids, 110 fewer than the wild type protein. Furthermore, the amino acid sequence was completely different between the mutant protein and the wild type protein starting from the 444th amino acid. Luciferase reporter assays revealed that the variant had impaired *HNF4A* promoter–regulation activity. The patient did not achieve good hypoglycemic effects during long-term treatment with insulin and metformin. The effect of hypoglycemic treatment was highly significant after the addition of sulfonylurea drugs.
Conclusions: The *HNF1A* p.Gln444fs variant associated with MODY3, and most likely a truncated protein, impaired *HNF1A* transcriptional activity. The variant carrier experienced an enhanced response to sulfonylureas.

1. Introduction

Diabetes mellitus affects approximately 9.3 % of the global population. It can be classified as type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and several other specific types of diabetes [1–5].

* Corresponding author.
** Corresponding author.
E-mail addresses: dapyxb@163.com (A. Deng), ljywxf110@163.com (J. Li).
[1] Xiufang Wang and Juyi Li contributed equally.

https://doi.org/10.1016/j.heliyon.2024.e35112
Received 9 April 2024; Received in revised form 18 July 2024; Accepted 23 July 2024
Available online 23 July 2024

Maturity-onset diabetes of the young (MODY), a specific type of diabetes and a type of monogenic diabetes, is an autosomal dominant inheritance caused by a single gene mutation [6,7] and is characterized by an early onset of younger than 25 years of age. While 14 genes have been designated as MODY genes, including *hepatic nuclear factor (HNF) 4A* (MODY1), *glucokinase* (*GCK*, MODY2), and *HNF1A* (MODY3) [6,7].

HNF1A (MODY3) on chromosome 12q, is mainly expressed in pancreatic beta cells, the intestines, and the liver, and plays an important role in regulating the cellular functions of glucose and lipid metabolism [8]. *HNF1A* is a protein containing 631 amino acids and has the following 3 functional domains: (1) the N-terminal dimerization domain, (2) the DNA-binding domains POU_S and POU_H, and (3) the C-terminal transactivation domain [9]. *HNF1A* binds to at least 106 target genes in pancreatic islets and to at least 222 target genes in hepatocytes [10]. To date, more than 500 *HNF1A* variations are known to lead to MODY3, and most of them are in the coding region. The mutation types include missense, nonsense, or frameshift mutations [8]. The HNF1A protein is synthesized in the cytoplasm and enters the nucleus as a transcription factor, regulating the expression of multiple genes in glucose metabolism and insulin secretion, such as *insulin promoter factor-1*, *HNF4A,* and *GLUT-2* [9]. Gradual damage of β cells having reduced insulin secretion is the hallmark of MODY3 (*HNF1A*) [11]. Patients with MODY3 typically exhibit urinary glucose due to reduced renal glucose reabsorption. MODY3 is typically diagnosed during adolescence or early adulthood. *HNF1A*-MODY occurs with lower body mass index, lower glycated hemoglobin (HbA1c), and triglycerides and has the risk of microvascular complications similar to that observed for type 2 diabetes. Multiple studies suggest that patients with MODY3 are sensitive to low-dose sulfonylureas (20–40 mg gliclazide daily) and that they can initially improve their glycemic control and quality of life through dietary modifications and sulfonylureas. However, additional treatment such as insulin is required at variable ages; therefore, phenomic studies on diseases and the precise diagnosis and treatment of MODY3 are very important [8,12–14].

In this study, we explored the pathogenic genes in this family, assessed the response to sulfonylureas, and investigated the functional characteristics of *HNF1A* mutations.

2. Materials and methods

2.1. Participants

The proband (IV-1) was a 14-year-old Chinese male who was diagnosed with type 2 diabetes at the age of 9 years. Physical examination revealed normal height and weight (150 cm and 35 kg, respectively), and the blood pressure and blood lipids were almost

Table 1
Demographics and Clinical Characteristics of the proband.

Laboratory (Normal range)	Test value
Age, y	14
T2D Duration, y	5
SBP, mm Hg	119
DBP, mm Hg	77
FPG, mmol/L	13.0
HbA1c, % (4–6)	15.5
HDL-C, mmol/L (>1.04)	0.88
LDL-C, mmol/L (<3.37)	1.92
TG, mmol/L (<1.7)	1.40
TC, mmol/L (<5.18)	3.32
Apo A, g/L (1.22–1.61)	0.98
Apo B, g/L (0.69–1.05)	0.75
Cr, μmol/L (57–97)	46.6
BUN, mmol/L (2.9–8.2)	3.56
UA, mmol/L (208–428)	325
pH (7.35–7.45)	7.39
C-reactive protein, mg/dL (0–0.6)	0.10
D-Dimer, μg/mL (0–1)	0.28
IAA, IU/mL (<20)	10.00
ICA, U/mL (0–29.79)	5.57
Anti-tyrosinase antibody, U/mL (0–28)	2.50
GAD-Ab, IU/mL (<30)	6.08
Glucose in urine (negative)	4+
Urinary ketone bodies (negative)	+-
Fasting C-peptide, ng/mL (0.69–2.45)	0.40
0.5 h-postprandial C-peptide, ng/mL (5–6 times the fasting C-peptide)	0.40
1 h-postprandial C-peptide, ng/mL (5–6 times the fasting C-peptide)	0.40
2 h-postprandial C-peptide, ng/mL (2–4 times the fasting C-peptide)	0.50

SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; Apo A, Apolipoprotein A; Apo B, Apolipoprotein B; Cr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; IAA: insulin autoantibodies; ICA: islet cell antibody; GAD-Ab: glutamic acid decarboxylase autoantibodies.

within the normal range (Table 1). He was prescribed acarbose, metformin, and insulin; however, his blood glucose control was very poor and his HbA1c was 15.5 %. The patient had intermittent nausea and vomiting for 3 days. He was physically healthy in the past and had no history of infectious diseases such as hepatitis B and no history of trauma, surgery, blood transfusion, or drug allergy. His body temperature was 36.1 °C, pulse was 80 per minute, and respiratory rate was 18 per minute. His mind was clear and there was no obvious swelling of the superficial lymph nodes. Slightly coarse breathing sounds were noted in both lungs but there were no obvious dry or wet rales; the rhythm of 80 bpm and rhythmic. Soft abdomen, no rebound pain, and no swelling were noted in both the lower limbs. Ultrasound showed no significant abnormalities in the abdomen, liver, and kidneys. The proband's mother and grandfather died due to unknown reasons from severe diabetes at ages 30 and 50 years, respectively. The proband's father and grandmother were enrolled in this study, and they had no history of diabetes. This study was approved by the Ethics Committee of Wuhan Central Hospital (2016-2). All participants signed an obtained form, ensuring compliance with ethical standards.

2.2. Whole-exome sequencing (WES)

Genomic DNA was isolated from peripheral blood [15], and library preparation was performed using the SureSelect Exome V5 Capture library. Sequencing was performed using a HiSeq2500 (Illumina) System, reaching an average depth of 100x [16].

2.3. Genetic analysis

All genetic variants reported in the text aligned with the GRCh37 (hg19) human reference, and the variant nomenclature complied with the recommendations of the Human Genomic Variation Society. The allele frequency referred to the following databases: Genome Aggregation database, Single Nucleotide Polymorphisms database, Exome Aggregation Consortium database, and the 1000 Genomes Project database. Variant annotation complied with the guidelines of the American College of Medical Genetics [17]. Variants were selected for data interpretation with minor allele frequencies <0.01 in the above databases [18]. Variants were classified into pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign groups [19]. Variants were filtered in the defined panel of the following 14 MODY genes: *ABCC8*, *APPL1*, *BLK*, *CEL*, *GCK*, *HNF1A*, *HNF1B*, *HNF4A*, *INS*, *KCNJ11*, *KLF11*, *NEUROD1*, *PAX4,* and *PDX1*. Lastly, the remaining deleterious variations in the patient were compared with his unaffected parents with the references of OMIM and the literature [19,20].

2.4. Sanger sequencing

Selected variants were validated. Polymerase chain reaction (PCR) was used to amplify gene fragments. Sanger sequencing was performed with the following primers: F 5′-TGGGCAGGGGTGGGATATAA-3′, R 5′-CCCTTTCCCCTGCATCCATT-3′. PCR products were purified and sequenced using Sanger sequencing (ABI 3730 XL DNA Analyzer). Based on the inheritance pattern, DNA samples of all participants were subjected to Sanger sequencing and segregation analysis.

2.5. Monitoring the clinical treatment outcomes after changing the drug therapy plan

Patients with *HNF1A* gene mutations were found to be more sensitive to sulfonylureas used to treat diabetes [21]. Blood glucose levels and HbA1c levels were regularly monitored after changing the drug therapy plan.

2.6. Plasmid information

The *HNF1A* wild type (WT) plasmid of human *HNF1A* (NM_000545.8, full-length cDNA) with a 3*Flag tag, whereas the *HNF1A* mutant type (MT, NM_000545.8:c.1330_1331del) plasmid contained the novel coding sequence with a 3*Flag tag. They were all cloned into the pcDNA3.1 vector. The part of the human *HNF4A* promoter (−1631 to −1431 bp) was synthesized and cloned into the pGL3-basic. Plasmids were constructed by Wuhan GeneCreate Biological Engineering Co., Ltd, China.

2.7. Cell culture and transfection

HEK-293T cells (ATCC CRL-11268, gift from Professor Jin Si and free of Mycoplasma. HEK-293T cells were authenticated immediately prior to conduct of experiments) were cultured in DMEM supplemented with 10 % fetal bovine serum. HEK-293T cells were transfected with the WT or MT *HNF1A* plasmids, or pcDNA3.1 vector, using a Lipofectamine 3000 kit (Thermo Fisher Scientific, USA) according to instruction.

2.8. Luciferase reporter assay

HEK-293T cells were seeded into 12-well culture plates, and each group was transfected separately with pRL-TK, pGL3-basic-*HNF4A*, and pcDNA3.1-WT-*HNF1A* or pcDNA3.1-MT-*HNF1A*. After 48 h transfection, luciferase activities were measured by a dual luciferase reporter assay kit (DL101-01, Vazyme, China).

3. Results

3.1. Medical history

The proband is a 14-year-old male admitted to the hospital for ketoacidosis. He was diagnosed with diabetes at the age of 9 years and had complaints of dry mouth, polydipsia, polyuria, and fatigue. He was prescribed acarbose, metformin, and insulin; however, ideal outcomes were not achieved. His HbA1c and fasting plasma glucose (FPG) levels were within the range of 12%–15.5 % and 9–25 mmol/L, respectively. The proband's mother (III-1) and grandfather (II-2) died due to unknown reasons from severe diabetes at the age of 30 and 50 years, respectively.

3.2. Clinical characteristics

The proband was admitted to the hospital with nausea and vomiting due to the irregular use of hypoglycemic drugs. Laboratory analysis (Table 1) revealed FPG level to be 13.0 mmol/L and HbA1c to be 15.5 %. He was positive for ketones and urine glucose, and his fasting C-peptide level was 0.4 ng/mL. His diabetic autoantibodies were all negative, and his blood pressure, serum lipid levels, and liver and renal functions were almost in the normal range. The pancreas, liver, kidneys, bladder, gall bladder, spleen, ureter were all in normal morphology by Ultrasound examination. The pedigree of the family is shown in Fig. 1. The proband's father (III-2), grandmother (II-1), and other relatives (II-3, III-3, and III-4) were all in good health.

3.3. Genetic and bioinformatics analyses

A total of 276546 variants were found using WES, including 250437 single nucleotide polymorphisms (SNPs) and 26109 insertion-deletions (InDels) (Table 2). Variants were filtered as previously described [22], a suspicious variant in *HNF1A* was found: frameshift deletion, chromosome 12, position 121435297–121435298, NM_000545.8:c.1330_1331del, NP_000536.6:p.Gln444fs, namely, rs776793516, which suggested the proband to be a known MODY3 type. In the SNP database, the frequency of the *HNF1A* p. Gln444fs mutation is very low (1/248382, GnomAD_exome; 1/115662, ExAC) and this mutation was pathogenic (Accession: VCV000617650.1). After genetic testing, healthy individuals II-1 and III-2 did not carry this mutation (Fig. 2), and the mutation site was co-segregated from diabetes.

3.4. Follow-up of the patient treated with sulfonylureas

Genetic testing confirmed the patient to be of the MODY3 subtype, which was recommended that the patient replace the treatment with current acarbose and metformin with sulfonylureas. However, considering that rapid changes in treatment may cause serious discomfort, gliclazide modified-release tablet (60 mg/day) was added to the patient's existing medications (Insulin Aspart 50 injection, 20 units before breakfast and 18 units before dinner daily; acarbose, 50 mg 3 times per day; metformin, 0.5 g at bedtime). After 3 months of treatment, his HbA1c level decreased from 15.5 % to 11.5 %, and after another 3 months of treatment, it dropped to 9.1 %. Although the current blood glucose levels were not well controlled, a significant hypoglycemic effect was achieved. Therefore, after the addition of gliclazide modified-release tablets, the patient's blood glucose levels improved significantly and he was found to be sensitive to sulfonylurea drugs.

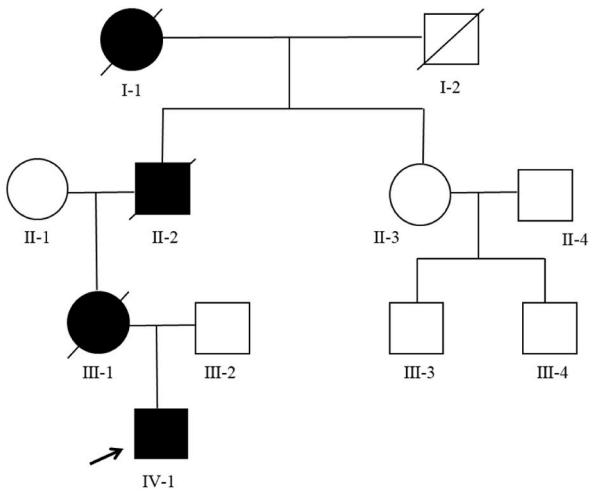

Fig. 1. Pedigree of the family of the proband. Circles represent women and squares represent men. Black symbols represent diabetes, slash indicates death, and the arrow represents the proband.

Table 2
Whole-exome sequencing detail of the proband.

Exome capture statistics	Proband
Total (bp)	160,981,146 (100 %)
Duplicate (bp)	39,846,546 (24.75 %)
Mapped (bp)	160,608,635 (99.77 %)
Properly mapped (bp)	158,585,020 (98.51 %)
PE mapped (bp)	160,347,464 (99.61 %)
SE mapped (bp)	522,342 (0.32 %)
Initial bases on target (bp)	60,456,963
Initial bases on or near target (bp)	136,297,444
Total effective yield (Mb)	16,007.56
Effective yield on target (Mb)	6755.12
Fraction of effective bases on target (%)	42.2 %
Fraction of effective bases on or near target (%)	61.4 %
Average sequencing depth on target	111.73
Bases covered on target (bp)	58,686,516
Coverage of target region (%)	97.1 %
Fraction of target covered with at least 100 × (%)	39.2 %
Fraction of target covered with at least 50 × (%)	66.7 %
Fraction of target covered with at least 10 × (%)	91.7
Total SNPs	250437
Novel SNPs	1434
Total InDels	26109
Novel InDels	3015
Gender	Male

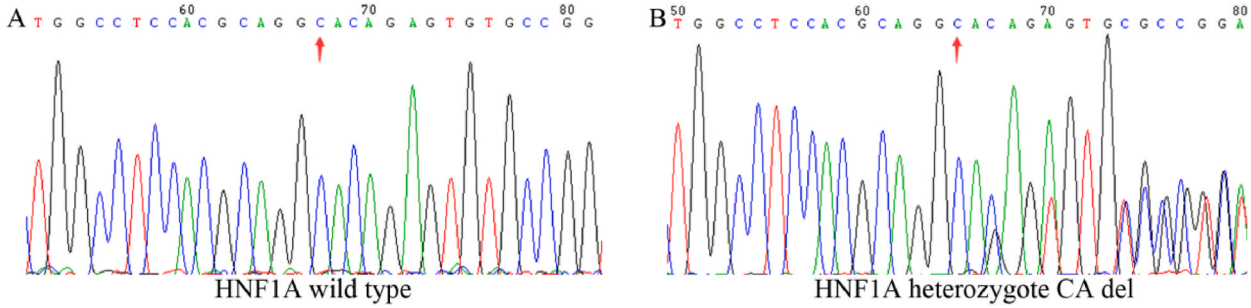

Fig. 2. Sequencing chromatogram. *HNF1A* variant (NM_000545.8:c.1330_1331 del, p.Gln444fs) was confirmed by Sanger sequencing. A: *HNF1A* wild type, only the base C; B: *HNF1A* heterozygote CA del.

3.5. HNF1A p.Gln444fs mutation decreases transcriptional activities in HEK-293T cells

HNF4A has been reported to be transcriptionally regulated by *HNF1A* [23]; therefore, it was used as the reporter gene. The mutant protein had 552 amino acids, which was 110 fewer than the WT protein. Between the mutant protein and the WT protein, the amino acid sequence was completely different starting from the 444th position (Fig. 3A). Compared with pcDNA3.1-WT-*HNF1A*, the transcriptional activity of pcDNA3.1-MT-*HNF1A* was significantly decreased in *HNF4A* (Fig. 3B), which may suggest that *HNF1A* p.Gln444fs mutation decreased transcriptional activity in HEK-293T cells (Fig. 3C).

4. Discussion

In this study, we report a 14-year-old boy with ketoacidosis (onset at the age of 9 years) and a germline *HNF1A* mutation (Hg19, Chr12: 121435297–121435298, NM_000545.8:c.1330_1331del, frameshift deletion, rs776793516). The patient's genetic test results showed that his blood glucose level decreased significantly after the addition of sulfonylureas. Furthermore, *HNF1A* p.Gln444fs mutation decreased transcriptional activity in HEK-293T cells.

MODY3 (*HNF1A* mutations) is the most common subtype of MODY. To date, more than 500 *HNF1A* mutations have been reported and up to 250 mutations are pathogenic [8]. *HNF1A* consists of amino-terminal dimerization, DNA-binding, and transactivation domains [24]. In *HNF1A,* P291fsinsC (p.G292fs) is the most frequent variation in MODY3. It lacks most of the transactivation domain, which leads to the loss of its transcriptional activity [25]. Several cases of rare *HNF1A* p.Gln444fs mutations have been reported in Europe and America [26–28]. However, this mutation is the first to be reported in Asia in this study, and there is no functional evidence in ClinVar for this variation. Moreover, the *HNF1A* p.Gln444fs mutation was similar to P291fsinsC (p.G292fs) and lacks part of the transactivation domain, which can affect its transcriptional activity. Furthermore, *HNF1A* is a transcription factor that is involved in

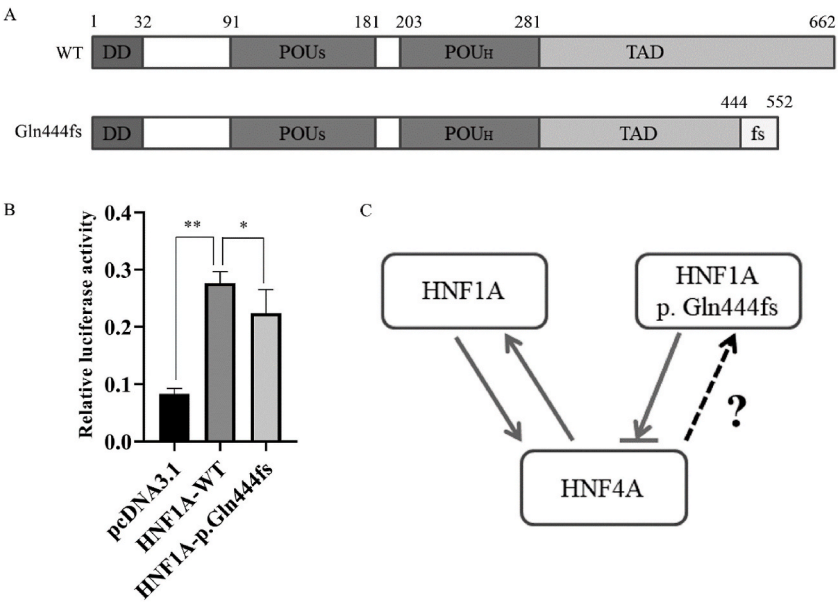

Fig. 3. Analysis of the transcriptional activities between wild type and mutant *HNF1A* on *HNF4A* promoters in HEK-293T cells. A: *HNF1A* gene structure. Dimerization domain (DD, amino acids 1–32); DNA-binding domain: POUs (amino acids 91–181) and POU_H (amino acids 203–279); transactivation domain (TAD, amino acids 281–662); frameshift: fs. B: Luciferase reporter analysis of *HNF4A* promoter activity overexpressed with pcDNA3.1, *HNF1A*-WT, and *HNF1A*-MT constructs (n = 5), $*P < 0.05$, $**P < 0.001$. C: Proposed relationship between *HNF4A* and *HNF1A*. *HNF4A* and *HNF1A* can bind and activate each other's promoter. However, *HNF1A* p.Gln444fs mutation decreased the transcriptional activities of *HNF4A* in HEK-293T cells. *HNF4A* might have also decreased the transcriptional activity of *HNF1A* p.Gln444fs.

the regulation of *HNF4A*, which plays a role in the maintenance of glucose homeostasis. Results from the dual-luciferase reporter assay indicated that *HNF1A* p.Gln444fs mutation decreased the transcriptional activities of *HNF4A* in HEK-293T. These findings suggested that *HNF1A* p.Gln444fs mutation impairs its transcriptional activity. However, the exact molecular mechanism underlying the influence of *HNF1A* p.Gln444fs mutations on the development of MODY3 should be determined in further prospective studies.

MODY3 (*HNF1A*) is the most common type of monogenic diabetes in Asia [29]. A deficiency in insulin secretion is the main clinical feature of MODY3 [30], which often leads to the misdiagnosis of type 1 or type 2 diabetes [31]. In this study, the C-peptide levels of the proband dropped to 0.4 ng/mL and the patient was treated for type 1 diabetes. After his blood glucose level was in better control, his C-peptide levels gradually returned to normal (0.94 ng/mL). Therefore, when blood glucose levels are not well controlled, the pancreatic islet function is severely damaged, similar to that seen in type 1 diabetes. For patients with MODY3, insulin and metformin might be the preferred pharmacological options. The proband was prescribed acarbose, metformin, and insulin; however, an ideal outcome was not achieved. Genome sequencing revealed that the proband to be the MODY3 type and he was highly sensitive to sulfonylurea drugs [32]. As the child was a minor, sulfonylurea drugs were added to his treatment regimen with the consent of his family members. During the 6 months of treatment and follow-up, his HbA1c level decreased from 15.5 % to 9.1 %. Despite his blood glucose level not reaching the normal level, good therapeutic effects were noted after commencing drug therapy. Thus, accurate diagnosis and suitable treatment regimens are crucial for patients with MODY3.

In conclusion, the data showed that the *HNF1A* p.Gln444fs variant associated with MODY3, and most likely a truncated protein, impairs *HNF1A* transcriptional activity. The variant carrier experiences an enhanced response to sulfonylureas.

Funding

This study has been supported by grants from the Central Guiding Local Science and Technology Development Special Project (grants no. 2022BGE272), Horizontal Subject (grants no. 2018404010261), and Guangdong Yiyang Healthcare Charity Foundation (grants no.JZ2022011).

Ethics statement

This study was approved by the Wuhan Central Hospital ethics committee (2016-2). Informed consent was obtained from the participants for the publication of clinical data and other data in this study.

Data availability statement

The data are available in article/supp. material/referenced in article and upon request.

CRediT authorship contribution statement

Xiufang Wang: Writing – review & editing, Writing – original draft, Investigation. **Wenzhuo Cheng:** Writing – review & editing, Writing – original draft, Validation. **Zhongjing Wang:** Writing – review & editing, Resources, Investigation. **Chao Liu:** Writing – review & editing, Project administration, Investigation, Data curation. **Aiping Deng:** Writing – review & editing, Validation, Project administration, Funding acquisition. **Juyi Li:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that there is no duality of interest associated with this manuscript.

Acknowledgments

We thank for the all participation in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35112.

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