Clin. Lab. 2024;70:XXX-XXX

CASE REPORT

A Novel KLF11 c.793G>A (p.Glu265Lys) Variant Identified in a Chinese Family with Controversial Association with MODY7

Lingyun Song [*], Di Sun [*], Ping Pang, Guoqing Yang

[*] *Lingyun Song and Di Sun contributed equally to this work as co-first authors*
Department of Endocrinology, Hainan Hospital of Chinese PLA General Hospital, Sanya, Hainan, China

SUMMARY

Background: **Krüppel-like 11 factor (KLF11) gene mutation has been implicated in the pathogenesis of maturity onset diabetes of the young type 7 (MODY7). Recently, this potential correlation has been questioned, suggesting the need for more comprehensive diagnostic approaches.**
Methods: **The proband is a 30-years-old male who underwent next-generation sequencing (NGS). This was followed by whole-exon sequencing of the proband and his parents to screen for KLF11 variants.**
Results: **A heterozygous KLF11 mutation c.793G>A (p.Glu265Lys) was identified in the proband and his non-diabetic mother.**
Conclusions: **The novel KLF11 mutation documented in this study might exhibit incomplete penetrance in relation to impaired glucose tolerance, which could also contribute to the argument against the necessity of including KLF11 genetic testing for MODY diagnosis.**
(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2024.240241)

Correspondence:
Guoqing Yang
Department of Endocrinology
Hainan Hospital of Chinese PLA General Hospital
Sanya, 572013
Hainan Province
China
Email: Guoqingyang301@126.com

Case Report accepted March 30, 2024

KEYWORDS

c.793G>A (p.Glu265Lys), Krüppel-like 11 factor (KLF11) gene, maturity onset diabetes of the young type 7 (MODY7), mutation, impaired glucose tolerance

CASE PRESENTATION

The proband was a 30-year-old male. In February 2019, during a routine physical examination, his fasting blood glucose level was elevated at 19 mmol/L. Despite not experiencing symptoms including thirst, excessive urination, or weight loss, he was referred to a nearby hospital and started to receive metformin treatment (0.25 g 3 times/day). The compliance of the proband was poor with his blood glucose level not monitored regularly. After nine months, the proband was admitted to our hospital for further diagnosis and treatment. Upon admission, his glycated hemoglobin A1c was 13.1%, indicating a poorly controlled blood glucose level. He also displayed ketonuria but tested negative for diabetes auto-antibodies and dyslipidemia. The proband's limosis, 1 hour, and 2 hour levels of blood glucose and in-

Table 1. Characteristics of Chinese MODY7 probands with KLF11 mutation reported in the literature. These case reports were published from February 2021 to December 2023.

Gender	Age (years)	Diabetes duration	Symptoms	BMI (kg/m^2)	KLF11 mutation locus	Treatment	Reference
Female	23	2 years	no	19.0	c.1061G>T, p.Cys354Phe	Gliclazide	Yujing et al. [5], Feb 2021
Male	9	2 months	yes	16.8	c.1045C>T, p.Pro349Ser	Insulin	Wu S et al. [4], June 2022
Male	32	13 years	yes	25.3	c.577C>A, p.Pro193Thr	Metformin, dulaglutide, dapagliflozin,	Guan G et al. [3], Nov 2022
Male	30	1 year	yes	22.5	c. G31A, p. D11N	Metformin	Zhang N et al. [9], Feb 2023
Male	30	9 months	yes	27.0	c.793G>A, p.Glu265Lys	Insulin and metformin	Current study, Dec 2023

BMI - body mass index.

sulin were determined: 1) blood glucose (mmol/L) were 20.52, 29.53, and 34.21, respectively; 2) Insulin (mU/L, normal range: 2.6 - 24.9 mU/L) were 9.19, 18.55, and 21.25, respectively. Additionally, the proband had a body mass index (BMI) of 27 kg/m^2. Physical examination revealed no significant abnormalities in his thyroid, heart, lungs, abdomen, peripheral nerves, and there was no lower limb edema.

His ketonuria quickly resolved after an effective fluid infusion and a low dose of intravenous insulin. We adjusted his long-term regimen to a combination of bedtime insulin glargine (30 units), pre-meal insulin injections (10 units before each meal), and oral metformin (0.5 g three times daily). Further blood glucose level measurement was done by the patient himself, and his blood glucose level was adequately controlled, reporting no further complications.

Family history

The proband demonstrated a family history of three generations of diabetes, suggesting a potential genetic mutation within the family (Figure 1A). His father was diagnosed with type 2 diabetes at 58 years old. Interestingly, the mother of the proband has no documented history of diabetes, and her blood glucose levels, measured several times at our hospital, were consistently normal. However, it is noteworthy that she has a low dietary intake, which could have masked potential abnormalities.

Genetic testing and methods

Due to the family history and abnormal lipid metabolism, type 2 diabetes was initially considered. However, the young age at diagnosis, diabetic ketosis, and the three-generation family history raised suspicion of a unique type of diabetes, such as MODY. The patient underwent whole-exome sequencing. Specifically, ethylenediaminetetraacetic acid (EDTA) anticoagulation was used to extract the genomic DNA from his peripheral blood leukocytes, which was then sent to Beijing San Valley Diagnostics Ltd. for sequencing. The coding regions of the human whole-exome were examined using high-throughput detection techniques. Following identification of the mutated gene and its location, Sanger sequencing was performed to confirm the mutated site. Blood samples of his parents were also sent to the test center, and the mutation site of the proband in them was tested using polymerase chain reaction (PCR)-Sanger sequencing validation technology.

RESULTS

The KLF11 c.793G>A (p.Glu265Lys) heterozygous mutation was determined in the proband. This mutation was also determined in his mother (Figure 1B). Moreover, we reviewed the case reports on KLF11 mutation focusing on the Chinese MODY7 patients (Table 1).

DISCUSSION

In 2005, Neve et al. first proposed that mutations in the KLF11 gene are associated with MODY7. The specific mutation site identified was KLF11 c.1039, G>T,P.Ala-347Ser, resulting in protein sequence changes that impair insulin synthesis [1]. A subsequent study conducted by Fernandez-Zapico et al. elucidated the potential core mechanism for the occurrence of MODY7, demonstrating that KLF11 is a pancreatic and duodenal homeobox 1 (PDX-1) transcriptional regulator dependent on P300, which can directly bind to the gene to exert transcriptional activation. This activation enables overexpression of the PDX-1 gene to promote insulin synthesis and maintain islet function [2]. While KLF11 mutations have been identified as the causative mutations for

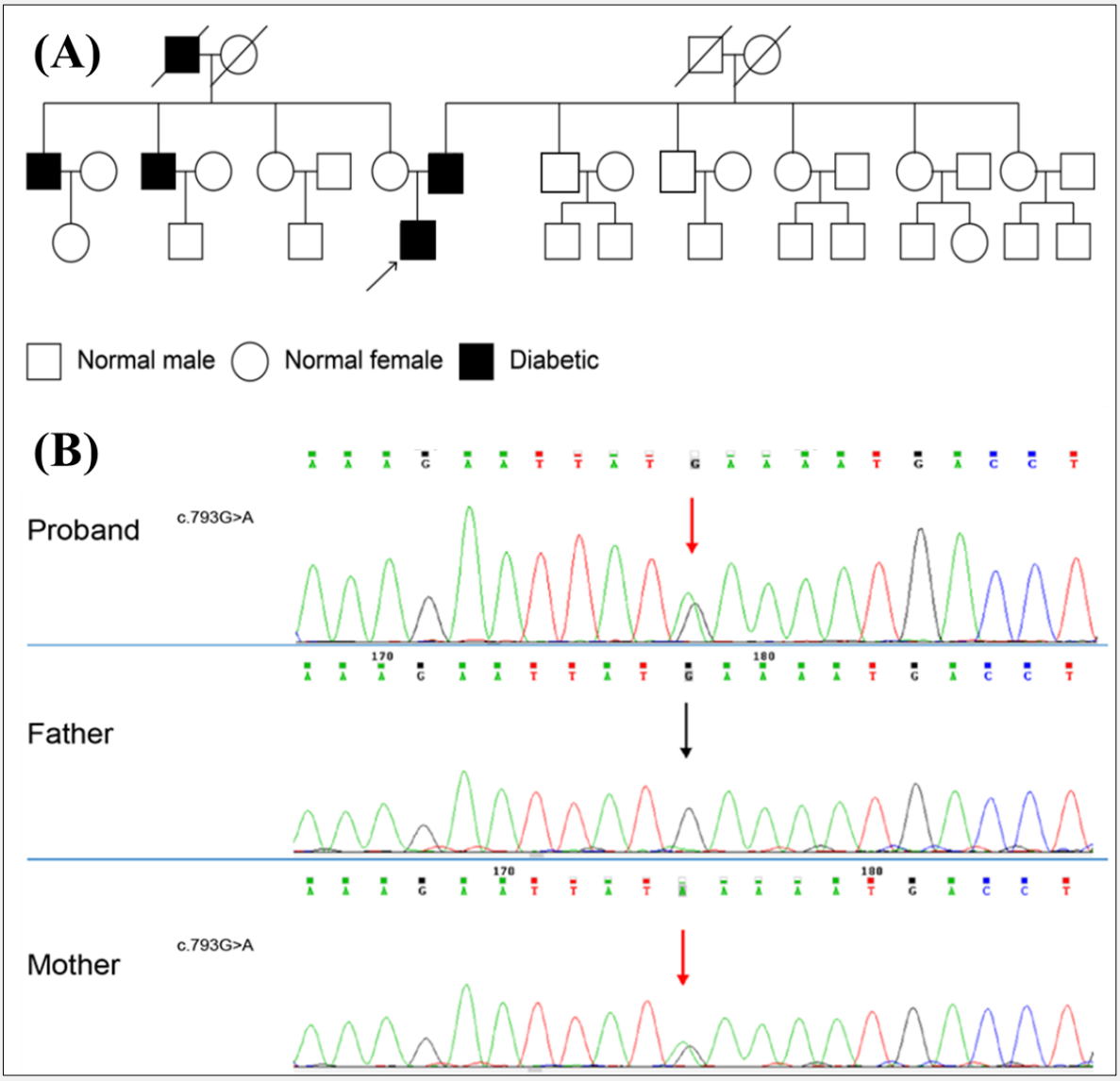

Figure 1. (A) The pedigree of the studied family members. Women are indicated with circles and men with squares. An arrow points out the proband. (B) Partial sequence diagram of KLF11 in the proband and his parents. A c.793G>A (p.Glu265 Lys) heterozygous mutation was identified in him and his mother.

MODY7, they are only found in certain variants in families with early-onset diabetes (5 in 27) [3]. Considering the rarity and unclear characteristics of MODY7, novel KLF11 variants could contribute to enhancing the current understanding of MODY7.

This study reported a novel KLF11 variant. Initially, the patient was highly suspected to have MODY7 based on the identification of a mutation in the KLF11 gene. However, the mutation was not found in the patient's diabetic father but was present in the patient's non-diabetic mother, suggesting an uncertain association of this specific mutation with MODY7. To understand why the mutation was present in his mother without causing diabetes, we reviewed the literature and discussed the following possibilities.

First, it is possible that the mutation exhibits incomplete penetrance and might have impaired glucose tolerance. To date, three cases of Chinese patients showed comparable situations to the case in our study. In 2021, Wu et al. reported a novel KLF11 variant potentially associ-

ated with MODY7 in a Chinese family where four family members have the mutation [4]. The proband and his mother had diabetes onset at a young age, 9 and 28 years, respectively. However, his maternal grandmother and an elderly aunt were not affected. Also, this year, Sun et al. reported another variant in a female proband diagnosed with MODY7 at age 23 [5]. This mutation was also found in her non-diabetic mother who has impaired glucose tolerance. Both studies demonstrated impaired insulin expression and secretion in pancreatic beta cells carrying the variant through *in vitro* analyses. Additionally, a recent study in 2023 reported a KLF11 variant with impaired glucose tolerance in a Chinese family, where three other cases with the mutation had diabetes mellitus which, with a high probability, was MODY7. It is worth noting that the proband's mother in this study had a consistently low-calorie diet, which might have increased liver insulin sensitivity, suggesting that her low-calorie diet lifestyle might influence her KLF11 expression status and normalized her blood glucose level in single measurements. Overall, we suggest that physicians consider conducting glucose tolerance test (OGTT) for individuals with KLF11 variants who do not exhibit signs of diabetes for early intervention.

Also, the mutation identified in our study could be a common mutation that does not directly cause MODY7. This possibility is supported by a recent study conducted by Laver et al., which challenges the necessity of KLF11 detection in MODY diagnosis [1]. Specifically, from 500,000 individuals, the frequency of two reported KLF11 variants was judged in only 313 normoglycemic individuals and 313 patients with type 2 diabetes. The enrichment of the variants was not observed in the MODY cohort. Further analysis suggested a poor cosegregation of KLF11, and the variants may act via gain of function, causing increased KLF11 repression activity. However, it is important to note that the study had limitations, including its cross-sectional design, the potential existence of a prolonged subclinical period for MODY7, and the limited number of variants analyzed. Therefore, a definitive conclusion cannot be made until more information is obtained through follow-up and testing of other important variants, including the ones described Sun et al. and Ushijima et al. [5,6]. Moreover, considering the prolonged pre-pathogenic period and the subclinical expression of the disease, [7] we recommend strict surveillance of glycemic control indicators and the appearance of microvascular complications in clinical practice for the diagnosis of MODY7.

Moreover, this study summarizes all the case reports of Chinese MODY7 probands with KLF11 mutations that are searchable on PubMed. Although the initial study where the KLF11 gene was related to the development of MODY7 was reported in 2005 [8], the first case report on a Chinese patient was presented in 2020 [9]. This fact might reveal the recently improved awareness and utility of NGS in disease diagnosis in China.

The limitations of this study should be addressed: 1) The compliance of the proband and his parents in the follow-up period is currently poor and limits the understanding of the effect of the mutation on their disease progression. 2) Not all members of this family were willing to be screened for the KLF11 mutation. If the proband's maternal uncles with diabetes have the mutation, it could consolidate the correlation of this variant with MODY7.

CONCLUSION

This study reported a novel KLF11 c.793G>A (p.Glu 265Lys) mutation variant that may be associated with the onset of MODY7. However, this association remains uncertain, as it was found in the proband's non-diabetic mother but not in his diabetic father. The incomplete penetrance of the mutation, especially regarding impaired glucose tolerance, and the possibility of the variant being a common mutation rather than a cause of MODY7 should be considered. Additionally, considering the limited number of reported MODY7 cases and possible long-term complications, subsequent follow-up is necessary for further diagnosis and pharmacological management of the patient.

Acknowledgment:
We would like to thank the participants involved in the study and Dr. Xue Wu for her assistance in medical editing.

Ethics Approval and Consent to Participate:
This study was strictly done in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Hainan Hospital of Chinese PLA General Hospital (No. 39). All participants signed the informed consent forms.

Availability of Data and Materials:
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding authors.

Declaration of Interest:
The authors declared no conflict of interest.

References:

1. Laver TW, Wakeling MN, Knox O, et al. Evaluation of Evidence for Pathogenicity Demonstrates That BLK, KLF11, and PAX4 Should Not Be Included in Diagnostic Testing for MODY. Diabetes 2022;71(5):1128-36. (PMID: 35108381)

2. Fernandez-Zapico ME, van Velkinburgh JC, Gutiérrez-Aguilar R, et al. MODY7 gene, KLF11, is a novel p300-dependent regulator of Pdx-1 (MODY4) transcription in pancreatic islet beta cells. J Biol Chem 2009;284(52):36482-90. (PMID: 19843526)

3. Guan G, Qin T, Zhao LL, Jin P. Genetic and Functional Analyses of the Novel KLF11 Pro193Thr Variant in a Three-Generation Family with MODY7. Horm Metab Res 2023;55(2):136-41. (PMID: 36241199)

4. Wu S, Zhang G, Liu L, Wu W, Luo X. A novel KLF11 variant in a family with maturity-onset diabetes of the young. Pediatr Diabetes 2022;23(5):597-603. (PMID: 35689450)

5. Sun Y, Qu J, Wang J, et al. Clinical and Functional Characteristics of a Novel KLF11 Cys354Phe Variant Involved in Maturity-Onset Diabetes of the Young. J Diabetes Res 2021;2021: 7136869. (PMID: 33604390)

6. Ushijima K, Narumi S, Ogata T, et al. KLF11 variant in a family clinically diagnosed with early childhood-onset type 1B diabetes. Pediatr Diabetes 2019;20(6):712-9. (PMID: 31124255)

7. Mancera-Rincón P, Camila Luna-España M, Rincon O, Guzmán I, Alvarez M. Maturity-onset Diabetes of the Young Type 7 (MODY7) and the Krüppel-like Factor 11 Mutation (KLF11). A review. Curr Diabetes Rev 2024;20(1):e210323214817. (PMID: 36944622)

8. Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V, et al. Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. Proc Natl Acad Sci U S A 2005;102(13): 4807-12. (PMID: 15774581)

9. Zhang N, Zhao H, Li C, Zhang FZ. Novel gene mutation in maturity-onset diabetes of the young: A case report. World J Clin Cases 2023;11(5):1099-105. (PMID: 36874436)