World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2023 July 15; 14(7): 1137-1145

DOI: 10.4239/wjd.v14.i7.1137

ISSN 1948-9358 (online)

CASE REPORT

Maturity-onset diabetes of the young type 9 or latent autoimmune diabetes in adults: A case report and review of literature

Guang-Hong Zhou, Min Tao, Qing Wang, Xing-Yu Chen, Jing Liu, Li-Li Zhang

Specialty type: Endocrinology and metabolism

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Yahaya TO, Nigeria; Yalcintepe S, Turkey

Received: December 17, 2022
Peer-review started: December 17, 2022
First decision: February 20, 2023
Revised: February 27, 2023
Accepted: June 5, 2023
Article in press: June 5, 2023
Published online: July 15, 2023

Guang-Hong Zhou, Min Tao, Qing Wang, Xing-Yu Chen, Jing Liu, Li-Li Zhang, Department of Endocrinology, The Second Affiliated Hospital, Chongqing Medical University, Chongqing 400010, China

Corresponding author: Li-Li Zhang, MD, PhD, Associate Professor, Doctor, Postdoc, Research Fellow, Department of Endocrinology, The Second Affiliated Hospital, Chongqing Medical University, No. 74 LinJiang Road, Yuzhong District, Chongqing 400010, China.
zhanglili.jl@foxmail.com

Abstract

BACKGROUND

Maturity-onset diabetes of the young (MODY) is a monogenic genetic disease often clinically misdiagnosed as type 1 or type 2 diabetes. MODY type 9 (MODY9) is a rare subtype caused by mutations in the *PAX4* gene. Currently, there are limited reports on *PAX4*-MODY, and its clinical characteristics and treatments are still unclear. In this report, we described a Chinese patient with high autoimmune antibodies, hyperglycemia and a site mutation in the *PAX4* gene.

CASE SUMMARY

A 42-year-old obese woman suffered diabetes ketoacidosis after consuming substantial amounts of beverages. She had never had diabetes before, and no one in her family had it. However, her autoantibody tested positive, and she managed her blood glucose within the normal range for 6 mo through lifestyle interventions. Later, her blood glucose gradually increased. Next-generation sequencing and Sanger sequencing were performed on her family. The results revealed that she and her mother had a heterozygous mutation in the *PAX4* gene (c.314G>A, p.R105H), but her daughter did not. The patient is currently taking liraglutide (1.8 mg/d), and her blood glucose levels are under control. Previous cases were retrieved from PubMed to investigate the relationship between *PAX4* gene mutations and diabetes.

CONCLUSION

We reported the first case of a *PAX4* gene heterozygous mutation site (c.314G>A, p.R105H), which does not appear pathogenic to MODY9 but may facilitate the progression of latent autoimmune diabetes in adults.

Key Words: Maturity-onset diabetes of the young; *PAX4*; Latent autoimmune diabetes in adults; Type 1 diabetes; Case report

Core Tip: Maturity-onset diabetes of the young type 9 (MODY9), as a subtype of MODY caused by mutations in the *PAX4* gene, has been poorly reported, and its clinical features and treatments remain unclear. We reported a heterozygous mutation in the *PAX4* gene (c.314G>A, p.R105H) in a patient with latent autoimmune diabetes in adults (LADA). Based on the analysis of the cases indexed in PubMed, it is the first reported case of *PAX4* with LADA. The *PAX4* heterozygous mutation reported in the present case may not be considered for MODY9 and may be facilitated for the onset and progress of LADA.

Citation: Zhou GH, Tao M, Wang Q, Chen XY, Liu J, Zhang LL. Maturity-onset diabetes of the young type 9 or latent autoimmune diabetes in adults: A case report and review of literature. *World J Diabetes* 2023; 14(7): 1137-1145
URL: https://www.wjgnet.com/1948-9358/full/v14/i7/1137.htm
DOI: https://dx.doi.org/10.4239/wjd.v14.i7.1137

INTRODUCTION

Maturity-onset diabetes of the young (MODY) is a monogenic genetic disease inherited predominantly and is often associated with impaired pancreatic β cell function[1,2]. The prevalence in adults is estimated to be 1 in 10000 and in children to be 1 in 23000, accounting for 1%-3% of diabetes cases[3,4]. A definitive diagnosis of MODY relies on genetic testing. According to the Standard of Care for Diabetes proposed in 2022[5], children diagnosed with diabetes within 6 mo or children or young adults who do not have typical characteristics of type 1 or type 2 diabetes but have a family history of diabetes for several generations should have genetic testing for MODY. MODY is often misdiagnosed as type 1 or type 2 diabetes[6,7].

MODY is classified into subtypes based on genetic mutations; 14 gene mutations have been proven to cause MODY. The most common types are *HNF4A*, *GCK* and *HNF1A*[8]. MODY9 is a subtype caused by mutations in the *PAX4* gene. *PAX4* belongs to the paired cassette homology domain family primarily expressed in pancreatic islets and is a key factor in the normal differentiation of β cells and δ cells[9]. Inactivation of *PAX4* causes a lack of mature β and δ cells in the pancreas, resulting in the body's inability to produce sufficient insulin and growth inhibitory hormone[10]. Numerous studies have shown that *PAX4* can promote the differentiation of stem cells to β cells[11,12], promote β cell survival and proliferation[13,14], induce the conversion of mature α cells to β cells[15,16], regulate cell cycle proteins[17] and maintain endoplasmic reticulum integrity[18] and other pathways that play a crucial role in diabetes. Reports on the diagnosis of *PAX4* mutations are still controversial, and the clinical features and treatment of *PAX4*-related hyperglycemia have not been identified. Here, we reported a patient with high autoimmune antibodies and hyperglycemia with a novel site mutation in the *PAX4* gene.

CASE PRESENTATION

Chief complaints

A 42-year-old woman presented with xerostomia, polydipsia, polyuria and blurred vision for 4 d.

History of present illness

The patient experienced xerostomia, polydipsia and polyuria after consuming substantial amounts of beverages and fruits 4 d before admission to the local hospital. She also had blurred vision and fatigue. She went to the local hospital, where her lab results revealed that her fasting blood glucose (FBG) was 18.15 mmol/L, and her glycated hemoglobin (HbA1c) was 10.3%. She was then prescribed metformin and another oral drug (details unknown) to control her blood glucose. However, her symptoms were not relieved, and her FBG remained at 14.54 mmol/L at the time of admission.

History of past illness

The patient had a history of cesarean section 18 years prior to admission and had uterine fibroids for 12 years.

Personal and family history

The patient reported no knowledge of diabetes in her family.

Physical examination

The patient was sane, conscious and had dry lips. Her body mass index was 31.85 kg/m^2, and her blood pressure was 133/96 mmHg. She was generally in good condition, and no other obvious abnormality was detected at admission.

Laboratory examinations

At admission, the patient arterial pH was 7.29, PO_2 was 93 mmHg, bicarbonate was 14.6 mmol/L, FBG was 14.54 mmol/L, islet cell antibody was 45 times higher than normal, glutamic acid decarboxylase (GAD) was 200 times higher than normal, and insulin autoantibody was two times higher than normal. Her urine ketone was significantly positive. Her liver function was slightly abnormal, but her blood lipids, albumin/creatinine ratio and thyroid function were normal (Table 1).

Next-generation sequencing

The patient was tested with next-generation sequencing (DNBSEQ-T7) to detect 130 genes related to diabetes, which include 14 pathogenic genes associated with MODY (*HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *ABCC8*, *KCNJ11*, *APPL1*). The patient's mother and daughter also underwent Sanger validation. The findings revealed that she had a heterozygous mutation in the *PAX4* gene (c.314G>A, p.R105H), and subsequent Sanger validation revealed that her mother also suffered the same mutation. Her daughter was normal (Figure 1).

FINAL DIAGNOSIS

Diabetic ketoacidosis and type 1 diabetes mellitus (T1DM).

TREATMENT

The patient was given a fluid replacement and insulin treatment at admission until her arterial pH and urine ketone levels returned to normal. She was then administered a hypodermic injection of mixed protamine zinc recombinant human insulin injection (70/30), 8 IU before breakfast and 8 IU before dinner, and her FBG level was 6-7 mmol/L at discharge. She maintained lifestyle interventions (balanced diet and regular exercise 30 min/d). One month after discharge, the patient discontinued insulin therapy, and her blood glucose appeared to be normal with lifestyle interventions.

OUTCOME AND FOLLOW-UP

The patient visited our outpatient clinic regularly for check-ups. She also regularly tested capsular blood glucose at home, and the data showed her blood glucose was well controlled. About 3 mo after discharge, we administered an oral glucose tolerance test (OGTT) to evaluate her cell function. Her HbA1c was 6.2%, OGTT (fasting, 30 min, 1 h and 2 h) was 5.96 mmol/L, 12.44 mmol/L, 12.64 mmol/L and 8.33 mmol/L, respectively, oral glucose-insulin release test (fasting, 30 min, 1 h and 2 h) was 6.82 μU/mL, 35.97 μU/mL, 44.81 μU/mL and 56.74 μU/mL, respectively, and the autoantibodies of GAD were still higher than the upper limit. At the 9-mo follow-up, she informed us that her capsular blood glucose was always around 7 mmol/L or slightly higher; hence, we further scheduled an HbA1c and an OGTT test. Her HbA1c was 7.3%, OGTT (fasting, 30 min, 1 h and 2 h) was 8.88 mmol/L, 11.26 mmol/L, 15.72 mmol/L and 18.17 mmol/L, respectively, and oral glucose-insulin release test (fasting, 30 min, 1 h and 2 h) was 11.93 μU/mL, 18.26 μU/mL, 30.93 μU/mL and 33.13 μU/mL. Furthermore, her GAD was still higher than the upper limit (GAD ≥ 10.0 IU/mL). Considering her gradually increasing blood glucose and relatively remaining cell function, she was administered liraglutide 1.8 mg once a day. Her fasting blood glucose was 5-6 mmol/L, and her postprandial blood glucose was 6-8 mmol/L (Figure 2).

DISCUSSION

Here, we reported a rare case of diabetes with a heterozygous mutation in the *PAX4* gene (c.314G>A, p.R105H). The patient, a middle-aged obese woman, had no obvious diabetic syndrome until she consumed substantial amounts of beverages and fruits. Her HbA1c was 10.3%, indicating that her blood glucose was increased for at least 3 mo. Her high body mass index and insidious onset diabetes are characteristics of type 2 diabetes. However, the repeated high level of autoantibodies (GAD, islet cell antibody and insulin autoantibody) suggested the diagnosis of latent autoimmune diabetes in adults (LADA). Furthermore, this was further supported by her short remission time after lifestyle interventions (about 3-6 mo) and progressive declining cell function and increased blood glucose. We performed genetic testing to exclude other reasons for hyperglycemia. We found that the patient and her mother had a heterozygous mutation in the *PAX4* gene (c.314G>A, p.R105H), while her daughter did not. We then drew her family pedigree (Figure 3), which confirmed that the mutation was indeed heterozygous, and the mother carried the mutation but with normal blood glucose. Therefore, we concluded that the mutation might not be the primary cause of her hyperglycemia. So, we did not diagnose her with MODY. To the best of our knowledge, this is the first case of LADA combined with a heterozygous mutation in the *PAX4* gene.

MODY9 is the result of a *PAX4* mutation. However, few studies have reported MODY9 in detail. Here, we conducted a literature review of case reports of *PAX4* mutation. We searched the PubMed database with the terms "maturity-onset

Table 1 Clinical features and laboratory results of the patient

Parameter	Values
Age at onset (yr)	42
Weight (kg)	79.5
Height (cm)	158
BMI (kg/m^2)	31.85
FBG (mmol/L)	14.54
HbA1c (%)	10.3
pH	7.29
HCO_3^- (mmol/L)	14.6
ABE	16.6
SBE	16.7
ICA (COI)	45.20
GAD (IU/mL)	> 2000.00
IAA (COI)	2.10
KET (mmol/L)	+-
UA (μmol/L)	484.7
TG (mmol/L)	1.23
TC (mmol/L)	4.22
HDL (mmol/L)	1.01
LDL (mmol/L)	2.89
ALT (U/L)	44.8
AST (U/L)	40.4
ALP (U/L)	66.6
GGT (U/L)	34.0

ABE: Actual base excess; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; FBG: Fasting blood glucose; GAD: Glutamic acid decarboxylase; GGT: γ-glutamyl transpeptidase; HbA1c: Glycated hemoglobin; HCO_3^-: Bicarbonate; HDL: High-density lipoprotein cholesterol; IAA: Insulin autoantibodies; ICA: Islet cell autoantibodies; KET: Urinary ketones; LDL: Low-density lipoprotein cholesterol; SBE: Standard base excess; TC: Total cholesterol; TG: Triglyceride; UA: Uric acid.

diabetes of the young or MODY" and "paired cassette homology domain or *PAX4*" and selected the case reports, pedigree analyses, and cross-sectional studies. If the article was not related to MODY9 or *PAX4* gene mutations, or if the specifics of the patient were not described, it was excluded. Finally, nine articles with 17 cases were included[19-27] (Table 2).

Of these cases, 6 cases[19,22,24,25] with heterozygous *PAX4* mutation and 1 case[20] with homozygous *PAX4* mutation were diagnosed with MODY, indicating that both homozygous and heterozygous mutations were pathogenic. However, in our case, the patient's mother had normal blood glucose, possibly because the present site mutation had little pathogenic function, or the mother may progress to diabetes in the future and have longer follow-up needs. The above 6 cases with heterozygous mutations had a family history, while the patient with the homozygous mutation had no family history. Moreover, our case also had no family history. Therefore, it is difficult to determine whether diabetic family history is a characteristic of *PAX4* mutation.

Six cases[21,26] were diagnosed with ketosis-prone diabetes, two-thirds of them were homozygous mutation, all were male, and most of them had a family history. One Japanese case of homozygous mutation[23] was diagnosed with type 2 diabetes mellitus (T2DM), and three Japanese cases of homozygous mutation[27] were diagnosed with late-onset diabetes. All of these patients were lean and had no obvious sex and family history differences. Of the 17 cases, only 1 female case with the homozygous mutation had a slightly high level of positive insulin antibody but with a relatively low HbA1c. She was treated with an oral drug and no detailed follow-ups; that case was diagnosed with late-onset diabetes.

Although the c.314G>A mutation has been reported in the dbSNP database, there is no article reporting the specific clinical features of the patients with this mutation nor has it been reported that this mutation is related to LADA. Therefore, our case is significant since it is the first to be reported in China with a mutation site and a high level of autoimmune antibodies. It had a 1-year follow-up to assess the changes in cell function and the progression of the

Table 2 Articles describing the characteristics of clinical cases carrying the *PAX4* mutant gene

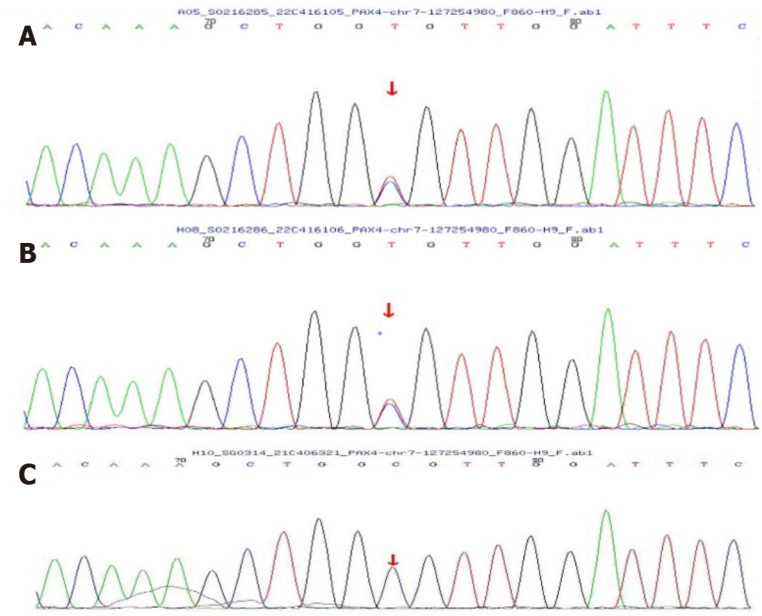
Ref.	Diagnosis	*PAX4* variant	Ethnicity	Family history	Diagnostic age (yr)	Sex	BMI (kg/m^2)	HbA1c, %	Insulin antibody, +/-	Treatment	HbA1c % at remission
Sujjitjoon *et al*[22]	MODY9	Heterozygous IVS7-1G>A	Thailand	Yes	44	Female	NA	NA	-	NA	NA
Chapla *et al* [25]	MODY	Heterozygous c.92G>T	Asian-Indian	Yes	14	Male	23	NA	-	Glimepiride and insulin	NA
Jo *et al*[19]	MODY	Heterozygous c.374-412 del 39	Japanese	Yes	15	Male	18.2	14.5	-	Insulin	7.4
Cho *et al* [20]	MODY	Homozygous c.575G>a	Korean	No	22	Male	25.3	13.8	NA	NA	NA
Abreu *et al* [24]	MODY	Heterozygous c.491G>A	Brazilian	Yes	32	Female	21.6	NA	-	Insulin	NA
			Brazilian	Yes	56	Female	29.48	11.3	-	Metformin and gliclazide	NA
			Brazilian	Yes	49	Female	23.61	6	-	Metformin	NA
Schmidt *et al*[21]	Ketosis-prone diabetes	Heterozygous c.109C>T	African	No	38	Male	28.4	> 14	-	Insulin	7.0
Mauvais-Jarvis *et al* [26]	Ketosis-prone diabetes	Homozygous R133W	West African	Yes	47	Male	29.1	13.8	-	Drugs	6.6
			West African	Yes	22	Male	18.5	12.2	-	Drugs	5.1
			West African	Yes	38	Male	28.3	14.1	-	Insulin	6.2
			West African	Yes	20	Male	26.5	12.5	-	Insulin	7.3
		Heterozygous R37W	West African	Yes	39	Male	30.4	11.6	-	Insulin	8.2
Kanatsuka *et al*[27]	Late-onset diabetic	Homozygous R121W	Japanese	Yes	37	Male	21.5	7.6	-	Insulin	NA
			Japanese	No	71	Male	22.8	7.1	-	Insulin	NA
			Japanese	Yes	71	Female	20.3	6.2	+	Drugs	NA
Shimajiri *et al*[23]	T2DM	Homozygous R121W	Japanese	No	29	Female	22.2	12.6	-	Insulin	7.3
Present case	T1DM	Heterozygous c.314G>A	Chinese	No	42	Female	31.85	10.3	+	Lifestyle control	7.3

BMI: Body mass index; MODY: Maturity-onset diabetes of the young; NA: Not available; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

disease.

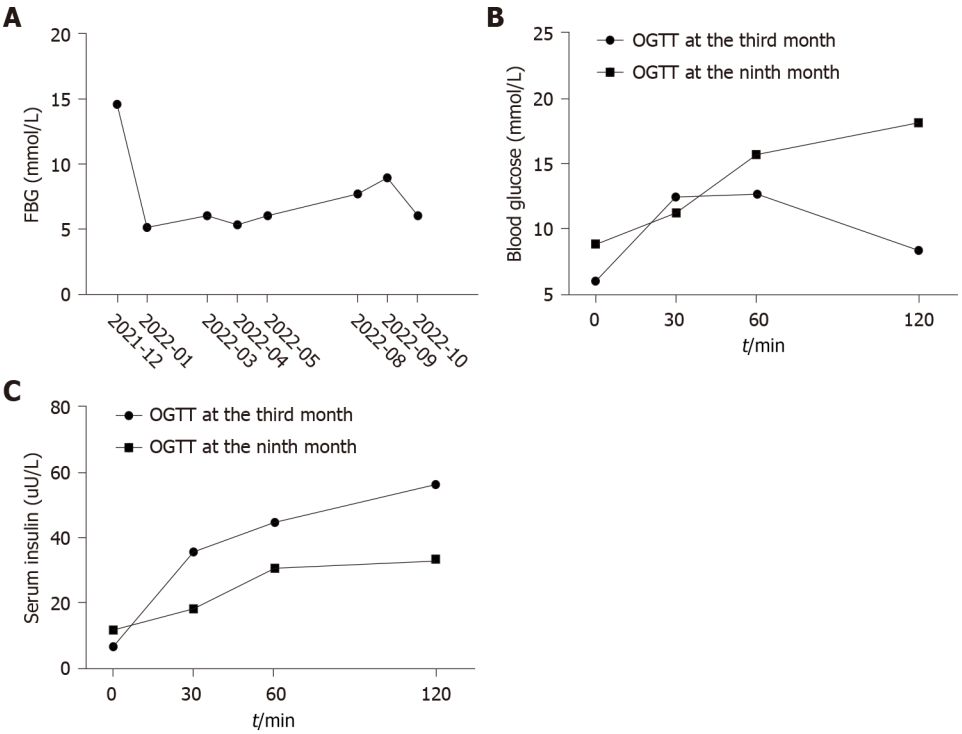
The literature on the diagnosis of *PAX4* mutation with hyperglycemia was controversial. Of the above 17 cases, only 1 case was diagnosed with MODY9, 6 cases were diagnosed only as MODY, and the other cases were diagnosed with ketosis-prone diabetes, late-onset diabetes and T2DM. No case was diagnosed as LADA. While cross-sectional studies found *PAX4* gene mutations to be associated with T2DM or ketosis-prone diabetes[21,23,26], population-based studies from China[28], Finland, Hungary[29] and the United Kingdom[30] found no significant association between the *PAX4* gene and the risk of developing T1DM. After Biason-Lauber *et al*[31] proposed that the *PAX4* variant 1168C>A was associated with T1DM, Geng *et al*[32] rejected this point the same year. Mechanically, *PAX4* plays a crucial role in the normal differentiation of β cells[9], including promoting the differentiation of stem cells to β cells[11,12], converting mature α cells to β cells[15,16] and maintaining β cell survival and proliferation[13,14]. Therefore, in our case, we considered that the heterozygous mutation in the *PAX4* gene might facilitate cell function decline, which coupled with autoimmune antibody destruction accelerates the progression of diabetes. However, this hypothesis also depends on the outcome of her mother's follow-up.

According to the treatment, in cases with mutations in the *PAX4* gene, 9 patients were treated with insulin (52.9%) and 6 patients with oral medication (35.3%). Liraglutide, an incretin hormone that can increase glucose-stimulated insulin secretion, has also been demonstrated to promote β cell proliferation, reduce apoptosis[33,34] and improve β cell function in high-lipid environments by activating the PI3K/Akt pathway[35]. For obese T1DM patients, clinical trials have



DOI: 10.4239/wjd.v14.i7.1137 **Copyright** ©The Author(s) 2023.

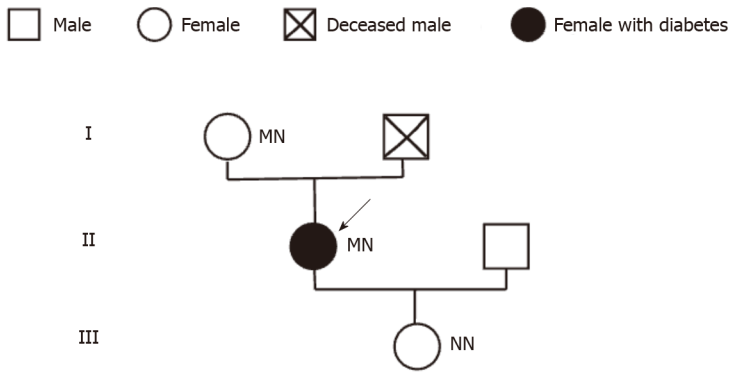
Figure 1 Sequencing profile of exon 5 of *PAX4* in the mutation region (R105H). A: Sequencing result of the propositus; B: Sequencing result of the mother; C: Sequencing result of the daughter. The whole exome sequencing and Sanger sequencing verification showed the propositus and her mother had the heterozygous variant of *PAX4*, c.314G>A; p.R105H, and the daughter was normal.



DOI: 10.4239/wjd.v14.i7.1137 **Copyright** ©The Author(s) 2023.

Figure 2 Changes of blood glucose and serum insulin during the follow-up. A: Fasting blood glucose levels from onset to follow-up; B: Oral glucose tolerance test levels during follow-up; C: Oral glucose-insulin release test levels during follow-up. FBG: Fasting blood glucose; OGTT: Oral glucose tolerance test; OGIRT: Oral glucose-insulin release test.

demonstrated that liraglutide can improve blood glucose, stimulate lipid oxidation and increase thermogenesis while maintaining lean body mass[36]. In T1DM patients with residual islet function, adjuvant therapy with liraglutide has also been proven to reduce HbA1c levels, reduce insulin requirements and increase C-peptide levels[37-39]. We finally added liraglutide to control blood glucose levels and was effectively controlling the patient's glucose levels at the last follow-up.



DOI: 10.4239/wjd.v14.i7.1137

Figure 3 Family pedigree of the patient. To the right of the symbol, it shows the genotype of *PAX4* c.314G>A mutation. M: Mutant allele; N: Normal allele.

CONCLUSION

In this report, we discovered a heterozygous mutation in *PAX4* (c.314G>A, p.R105H) that can coexist with LADA and does not appear pathogenic to MODY9 but may facilitate the progression of LADA. Further functional experiments are needed to confirm this in future.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the patient and family members that agreed to participate in this study.

FOOTNOTES

Author contributions: Zhou GH and Tao M contributed to manuscript writing and editing; Chen XY, Wang Q and Liu J contributed to data collection and analysis; Zhang LL contributed to conceptualization and supervision; All authors read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 81300702; and the Natural Science Foundation Project of Chongqing CSTC, No. cstc2018jcyjAXO210.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Guang-Hong Zhou 0000-0001-8775-1998; Min Tao 0000-0001-5804-1671; Qing Wang 0000-0002-7972-6423; Xing-Yu Chen 0000-0003-0244-3721; Jing Liu 0000-0002-5189-4644; Li-Li Zhang 0000-0001-9007-5281.

S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Zhang H

REFERENCES

1 **Yorifuji T**, Kurokawa K, Mamada M, Imai T, Kawai M, Nishi Y, Shishido S, Hasegawa Y, Nakahata T. Neonatal diabetes mellitus and

neonatal polycystic, dysplastic kidneys: Phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. *J Clin Endocrinol Metab* 2004; **89**: 2905-2908 [PMID: 15181075 DOI: 10.1210/jc.2003-031828]

2 **Stanik J**, Dusatkova P, Cinek O, Valentinova L, Huckova M, Skopkova M, Dusatkova L, Stanikova D, Pura M, Klimes I, Lebl J, Gasperikova D, Pruhova S. De novo mutations of GCK, HNF1A and HNF4A may be more frequent in MODY than previously assumed. *Diabetologia* 2014; **57**: 480-484 [PMID: 24323243 DOI: 10.1007/s00125-013-3119-2]

3 **Pihoker C**, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, Greenbaum CJ, Imperatore G, Lawrence JM, Marcovina SM, Mayer-Davis E, Rodriguez BL, Steck AK, Williams DE, Hattersley AT; SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. *J Clin Endocrinol Metab* 2013; **98**: 4055-4062 [PMID: 23771925 DOI: 10.1210/jc.2013-1279]

4 **Shepherd M**, Shields B, Hammersley S, Hudson M, McDonald TJ, Colclough K, Oram RA, Knight B, Hyde C, Cox J, Mallam K, Moudiotis C, Smith R, Fraser B, Robertson S, Greene S, Ellard S, Pearson ER, Hattersley AT; UNITED Team. Systematic Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. *Diabetes Care* 2016; **39**: 1879-1888 [PMID: 27271189 DOI: 10.2337/dc16-0645]

5 **American Diabetes Association**. Introduction: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; **45** (Suppl 1): S1-S2 [PMID: 34964812 DOI: 10.2337/dc22-Sint]

6 **Shields BM**, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia* 2010; **53**: 2504-2508 [PMID: 20499044 DOI: 10.1007/s00125-010-1799-4]

7 **Petruzelkova L**, Dusatkova P, Cinek O, Sumnik Z, Pruhova S, Hradsky O, Vcelakova J, Lebl J, Kolouskova S. Substantial proportion of MODY among multiplex families participating in a Type 1 diabetes prediction programme. *Diabet Med* 2016; **33**: 1712-1716 [PMID: 26641800 DOI: 10.1111/dme.13043]

8 **Urbanova J**, Brunerova L, Broz J. Hypoglycemia and antihyperglycemic treatment in adult MODY patients - A systematic review of literature. *Diabetes Res Clin Pract* 2019; **158**: 107914 [PMID: 31682881 DOI: 10.1016/j.diabres.2019.107914]

9 **Lenoir O**, Flosseau K, Ma FX, Blondeau B, Mai A, Bassel-Duby R, Ravassard P, Olson EN, Haumaitre C, Scharfmann R. Specific control of pancreatic endocrine β- and δ-cell mass by class IIa histone deacetylases HDAC4, HDAC5, and HDAC9. *Diabetes* 2011; **60**: 2861-2871 [PMID: 21953612 DOI: 10.2337/db11-0440]

10 **Sosa-Pineda B**, Chowdhury K, Torres M, Oliver G, Gruss P. The Pax4 gene is essential for differentiation of insulin-producing beta cells in the mammalian pancreas. *Nature* 1997; **386**: 399-402 [PMID: 9121556 DOI: 10.1038/386399a0]

11 **Açiksari A**, Duruksu G, Karaöz E. Improved insulin-secreting properties of pancreatic islet mesenchymal stem cells by constitutive expression of Pax4 and MafA. *Turk J Biol* 2017; **41**: 979-991 [PMID: 30814862 DOI: 10.3906/biy-1707-79]

12 **Liew CG**, Shah NN, Briston SJ, Shepherd RM, Khoo CP, Dunne MJ, Moore HD, Cosgrove KE, Andrews PW. PAX4 enhances beta-cell differentiation of human embryonic stem cells. *PLoS One* 2008; **3**: e1783 [PMID: 18335054 DOI: 10.1371/journal.pone.0001783]

13 **Parajuli KR**, Zhang Y, Cao AM, Wang H, Fonseca VA, Wu H. Pax4 Gene Delivery Improves Islet Transplantation Efficacy by Promoting β Cell Survival and α-to-β Cell Transdifferentiation. *Cell Transplant* 2020; **29**: 963689720958655 [PMID: 33086892 DOI: 10.1177/0963689720958655]

14 **Brun T**, Franklin I, St-Onge L, Biason-Lauber A, Schoenle EJ, Wollheim CB, Gauthier BR. The diabetes-linked transcription factor PAX4 promotes {beta}-cell proliferation and survival in rat and human islets. *J Cell Biol* 2004; **167**: 1123-1135 [PMID: 15596543 DOI: 10.1083/jcb.200405148]

15 **Collombat P**, Xu X, Ravassard P, Sosa-Pineda B, Dussaud S, Billestrup N, Madsen OD, Serup P, Heimberg H, Mansouri A. The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells. *Cell* 2009; **138**: 449-462 [PMID: 19665969 DOI: 10.1016/j.cell.2009.05.035]

16 **Al-Hasani K**, Pfeifer A, Courtney M, Ben-Othman N, Gjernes E, Vieira A, Druelle N, Avolio F, Ravassard P, Leuckx G, Lacas-Gervais S, Ambrosetti D, Benizri E, Hecksher-Sorensen J, Gounon P, Ferrer J, Gradwohl G, Heimberg H, Mansouri A, Collombat P. Adult duct-lining cells can reprogram into β-like cells able to counter repeated cycles of toxin-induced diabetes. *Dev Cell* 2013; **26**: 86-100 [PMID: 23810513 DOI: 10.1016/j.devcel.2013.05.018]

17 **Lee G**, Jang H, Kim YY, Choe SS, Kong J, Hwang I, Park J, Im SS, Kim JB. SREBP1c-PAX4 Axis Mediates Pancreatic β-Cell Compensatory Responses Upon Metabolic Stress. *Diabetes* 2019; **68**: 81-94 [PMID: 30352876 DOI: 10.2337/db18-0556]

18 **Mellado-Gil JM**, Jiménez-Moreno CM, Martin-Montalvo A, Alvarez-Mercado AI, Fuente-Martin E, Cobo-Vuilleumier N, Lorenzo PI, Bru-Tari E, Herrera-Gómez Ide G, López-Noriega L, Pérez-Florido J, Santoyo-López J, Spyrantis A, Meda P, Boehm BO, Quesada I, Gauthier BR. PAX4 preserves endoplasmic reticulum integrity preventing beta cell degeneration in a mouse model of type 1 diabetes mellitus. *Diabetologia* 2016; **59**: 755-765 [PMID: 26813254 DOI: 10.1007/s00125-016-3864-0]

19 **Jo W**, Endo M, Ishizu K, Nakamura A, Tajima T. A novel PAX4 mutation in a Japanese patient with maturity-onset diabetes of the young. *Tohoku J Exp Med* 2011; **223**: 113-118 [PMID: 21263211 DOI: 10.1620/tjem.223.113]

20 **Cho YK**, Lee JM, Song G, Choi HS, Cho EH, Kim SW. The ominous trio of PCSK1, CHD7 and PAX4: Normosmic hypogonadotropic hypogonadism with maturity-onset diabetes in a young man. *Clin Endocrinol (Oxf)* 2020; **92**: 554-557 [PMID: 32171037 DOI: 10.1111/cen.14182]

21 **Schmidt W**, Lankers H. Co-inheritance of PAX4 and BLK Mutations (MODY 7 and 9) in an 38 Year old African Patient with Ketosis-Prone Diabetes. Gemeinschaftspraxis für Humangenetik & Genetische Labore 2016 [DOI: 10.1530/ENDOABS.41.EP401]

22 **Sujjitjoon J**, Kooptiwut S, Chongjaroen N, Tangjittipokin W, Plengvidhya N, Yenchitsomanus PT. Aberrant mRNA splicing of paired box 4 (PAX4) IVS7-1G>A mutation causing maturity-onset diabetes of the young, type 9. *Acta Diabetol* 2016; **53**: 205-216 [PMID: 25951767 DOI: 10.1007/s00592-015-0760-x]

23 **Shimajiri Y**, Sanke T, Furuta H, Hanabusa T, Nakagawa T, Fujitani Y, Kajimoto Y, Takasu N, Nanjo K. A missense mutation of Pax4 gene (R121W) is associated with type 2 diabetes in Japanese. *Diabetes* 2001; **50**: 2864-2869 [PMID: 11723072 DOI: 10.2337/diabetes.50.12.2864]

24 **Abreu GM**, Soares CAPD, Tarantino RM, da Fonseca ACP, de Souza RB, Pereira MFC, Cabello PH, Rodacki M, Zajdenverg L, Zembrzuski VM, Campos Junior M. Identification of the First PAX4-MODY Family Reported in Brazil. *Diabetes Metab Syndr Obes* 2020; **13**: 2623-2631 [PMID: 32801813 DOI: 10.2147/DMSO.S256858]

25 **Chapla A**, Mruthyunjaya MD, Asha HS, Varghese D, Varshney M, Vasan SK, Venkatesan P, Nair V, Mathai S, Paul TV, Thomas N. Maturity onset diabetes of the young in India - a distinctive mutation pattern identified through targeted next-generation sequencing. *Clin Endocrinol (Oxf)* 2015; **82**: 533-542 [PMID: 25041077 DOI: 10.1111/cen.12541]

26 **Mauvais-Jarvis F**, Smith SB, Le May C, Leal SM, Gautier JF, Molokhia M, Riveline JP, Rajan AS, Kevorkian JP, Zhang S, Vexiau P,

German MS, Vaisse C. PAX4 gene variations predispose to ketosis-prone diabetes. *Hum Mol Genet* 2004; **13**: 3151-3159 [PMID: 15509590 DOI: 10.1093/hmg/ddh341]

27 **Kanatsuka A**, Tokuyama Y, Nozaki O, Matsui K, Egashira T. Beta-cell dysfunction in late-onset diabetic subjects carrying homozygous mutation in transcription factors NeuroD1 and Pax4. *Metabolism* 2002; **51**: 1161-1165 [PMID: 12200761 DOI: 10.1053/meta.2002.34707]

28 **Zhang Y**, Xiao X, Liu Y, Zhu X, Wenhui L, Li N, Yuan T, Wang H. The association of the PAX4 gene with type 1 diabetes in Han Chinese. *Diabetes Res Clin Pract* 2008; **81**: 365-369 [PMID: 18617287 DOI: 10.1016/j.diabres.2008.05.009]

29 **Hermann R**, Mantere J, Lipponen K, Veijola R, Soltesz G, Otonkoski T, Simell O, Knip M, Ilonen J. Lack of association of PAX4 gene with type 1 diabetes in the Finnish and Hungarian populations. *Diabetes* 2005; **54**: 2816-2819 [PMID: 16123375 DOI: 10.2337/diabetes.54.9.2816]

30 **Martin RJ**, Savage DA, Carson DJ, Maxwell AP, Patterson CC. The PAX4 gene variant A1168C is not associated with early onset Type 1 diabetes in a UK population. *Diabet Med* 2006; **23**: 927-928 [PMID: 16911636 DOI: 10.1111/j.1464-5491.2006.01869.x]

31 **Biason-Lauber A**, Boehm B, Lang-Muritano M, Gauthier BR, Brun T, Wollheim CB, Schoenle EJ. Association of childhood type 1 diabetes mellitus with a variant of PAX4: possible link to beta cell regenerative capacity. *Diabetologia* 2005; **48**: 900-905 [PMID: 15834548 DOI: 10.1007/s00125-005-1723-5]

32 **Geng DG**, Liu SY, Steck A, Eisenbarth G, Rewers M, She JX. Comment on: Biason-Lauber A, Boehm B, Lang-Muritano M, *et al* (2005) Association of childhood type 1 diabetes mellitus with a variant of PAX4: possible link to beta cell regenerative capacity. Diabetologia 48:900-905. *Diabetologia* 2006; **49**: 215-216 [PMID: 16362282 DOI: 10.1007/s00125-005-0064-8]

33 **Tamura K**, Minami K, Kudo M, Iemoto K, Takahashi H, Seino S. Liraglutide improves pancreatic Beta cell mass and function in alloxan-induced diabetic mice. *PLoS One* 2015; **10**: e0126003 [PMID: 25938469 DOI: 10.1371/journal.pone.0126003]

34 **Ding M**, Fang QH, Cui YT, Shen QL, Liu Q, Wang PH, Yu DM, Li CJ. Liraglutide prevents β-cell apoptosis *via* inactivation of NOX2 and its related signaling pathway. *J Diabetes Complications* 2019; **33**: 267-277 [PMID: 30772113 DOI: 10.1016/j.jdiacomp.2018.12.013]

35 **Shao S**, Nie M, Chen C, Chen X, Zhang M, Yuan G, Yu X, Yang Y. Protective action of liraglutide in beta cells under lipotoxic stress *via* PI3K/Akt/FoxO1 pathway. *J Cell Biochem* 2014; **115**: 1166-1175 [PMID: 24415347 DOI: 10.1002/jcb.24763]

36 **Ghanim H**, Batra M, Green K, Abuaysheh S, Hejna J, Makdissi A, Borowski R, Kuhadiya ND, Chaudhuri A, Dandona P. Liraglutide treatment in overweight and obese patients with type 1 diabetes: A 26-week randomized controlled trial; mechanisms of weight loss. *Diabetes Obes Metab* 2020; **22**: 1742-1752 [PMID: 32424935 DOI: 10.1111/dom.14090]

37 **Kuhadiya ND**, Prohaska B, Ghanim H, Dandona P. Addition of glucagon-like peptide-1 receptor agonist therapy to insulin in C-peptide-positive patients with type 1 diabetes. *Diabetes Obes Metab* 2019; **21**: 1054-1057 [PMID: 30536789 DOI: 10.1111/dom.13609]

38 **Dejgaard TF**, Frandsen CS, Hansen TS, Almdal T, Urhammer S, Pedersen-Bjergaard U, Jensen T, Jensen AK, Holst JJ, Tarnow L, Knop FK, Madsbad S, Andersen HU. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2016; **4**: 221-232 [PMID: 26656289 DOI: 10.1016/S2213-8587(15)00436-2]

39 **Dejgaard TF**, Schmidt S, Frandsen CS, Vistisen D, Madsbad S, Andersen HU, Nørgaard K. Liraglutide reduces hyperglycaemia and body weight in overweight, dysregulated insulin-pump-treated patients with type 1 diabetes: The Lira Pump trial-a randomized, double-blinded, placebo-controlled trial. *Diabetes Obes Metab* 2020; **22**: 492-500 [PMID: 31696598 DOI: 10.1111/dom.13911]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com