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

Zhou *et al*. MODY9 or LADA

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## 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 six months 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

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**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 *PAX4* gene heterozygous mutation (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.

## 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[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 six months 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-cell and δ-cell[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 cells 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 to play a crucial role in diabetes. Reports on the diagnosis of *PAX4* mutation are still controversial, and the clinical features and treatment of *PAX4*-related hyperglycemia have not been identified. Here, we report a patient with high autoimmune antibodies and hyperglycemia with a novel site mutation in the *PAX4* gene.

## CASE PRESENTATION

### *Imaging examinations*

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*), and her mother and daughter 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; however, her daughter was normal (Figure 1).

***Laboratory examinations***

At admission, her arterial pH was 7.29, $PO_2$ was 93 mmHg, $HCO_3^-$ was 14.6 mmol/L, fasting blood glucose (FBG) was 14.54 mmol/L, islet cell antibody (ICA) was 45 times higher than normal, glutamic acid decarboxylase (GAD) was 200 times higher than normal, and insulin autoantibody (IAA) was twice higher than normal. Her urine ketone was significantly positive. Her liver function was a little abnormal, but her blood lipids, albumin/creatinine ratio, and thyroid function were normal (Table 1).

***Physical examination***

She was sane, conscious, and had dry lips. Her body mass index (BMI) 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.

***Personal and family history***

No diabetes was reported in her family.

***History of past illness***

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

***History of present illness***

The patient felt xerostomia, polydipsia, and polyuria after consuming substantial amounts of beverages and fruits four days 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 FBG was 18.15 mmol/L and her HbA1c was 10.3%. She was then prescribed metformin and another oral drug (details unknown) to control her blood glucose. However, her symptoms did not relieve, and her FBG remained at 14.54 mmol/L at the time of admission.

***Chief complaints***

A 42-year-old woman was presented with xerostomia, polydipsia, polyuria, and blurred vision for four days.

**FINAL DIAGNOSIS**

Diabetic ketoacidosis and type 1 diabetes mellitus (T1DM).

**TREATMENT**

She 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), 8iu before breakfast and 8iu/before dinner, and her fasting blood glucose level was 6-7 mmol/L at discharge. She maintained lifestyle intervention (balanced diet and regular exercise, half an hour a day), and about one month after discharge, the patient discontinued insulin therapy and her blood glucose appeared to be normal under lifestyle intervention.

**OUTCOME AND FOLLOW-UP**

She 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 three months later, we gave an oral glucose tolerance test (OGTT) to evaluate her beta cell function. Her HbA1c was 6.2%, OGTT (0 min-30 min-1 h-2 h) was 5.96-12.44-12.64-8.33 mmol/L, oral glucose-insulin release test (OGIRT) (fasting-30 min-

1 h-2 h) was 6.82-35.97-44.81-56.74 uU/mL, and the autoantibodies of GAD was 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-2 h) was 8.88-11.26-15.72-18.17 mmol/L, OGIRT (fasting-30 min-1 h-2 h) was 11.93-18.26-30.93-33.13 uU/mL. Furthermore, her GAD was still higher than the upper limit in our lab (GAD ≥ 10.0 IU/mL). Considering her gradually increasing blood glucose and relatively remaining beta 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 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 three months. Her high BMI and insidious onset diabetes are characteristics of type 2 diabetes. However, the repeated high level of autoantibodies (GAD, ICA, and IAA) suggested the diagnosis of latent autoimmune diabetes in adults (LADA). Furthermore, this was further supported by her short time remission by lifestyle intervention (about 3-6 mo) and progressively declined beta cell function and increased blood glucose. We performed genetic testing to exclude other reasons for her 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 didn't. We then drew her family pedigree (Figure 3), which confirmed that the mutation is indeed heterozygous and the mother carrying 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 was 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 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, six cases[19,22,24,25] with heterozygous *PAX4* mutation and one 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 a little pathogenic function or the mother may progress to diabetes in the future and have longer follow-up needs. All the above six 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 hard to say that diabetic family history is the 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 all the 17 cases, only one female case with the homozygous mutation had a slightly high level of positive insulin antibody but with a relatively low HbA1c and was treated with the oral drug and no detailed follow-ups; that case was diagnosed with late-onset diabetes. Although c.314G>A mutation has been reported in the dbSNP database, there is still no article reporting the specific clinical feathers of the patients with this mutation, nor has it been reported that this mutation can be combined with LADA. So 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 one-year follow-up to assess the changes in beta cell function and the progression of the disease.

The literature on the diagnosis of *PAX4* mutation with hyperglycemia was controversial. Of those above 17 cases, only one was diagnosed as MODY9, six were diagnosed only as MODY, and all others 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 type 2 diabetes 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-cell[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 cells survival and proliferation[13,14]. Therefore, in our case, we considered that the heterozygous mutation in the *PAX4* gene might facilitate the beta cell function declination, which, coupled with autoimmune antibody destruction, accelerates the progression of diabetes. However, it also depends on the outcome of her mother's follow-up.

According to the treatment, in cases with mutations in the *PAX4* gene, nine patients were treated with insulin (52.9%) and six 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 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 it seemed to work well up to the last follow-up.

## 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.

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