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CASE REPORT

Pedigree Analysis of Maturity-Onset Diabetes of the Young: ABCC8 Mutations?

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SUMMARY

Background: **Maturity-Onset Diabetes of the Young (MODY) is an autosomal dominant disease, caused by mutations in the ABCC8 gene, chromosome 11.**
Methods: **A case suspected of MODY due to an ABCC8 mutation was examined using whole-genome exon high-throughput sequencing. Selected variant sites were validated via Sanger sequencing.**
Results: **A heterozygous mutation c.2060C>T (p.T687M) in exon 15 of the ABCC8 gene (Chr11-174494701) was identified in both the proband and the father. This mutation was initially linked to MODY based on clinical features.**
Conclusions: **For patients with high suspicion of MODY, genetic test should conducted to improve their quality of life.**
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KEYWORDS

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INTRODUCTION

Maturity-Onset Diabetes of the Young (MODY) presenting in adolescence shares clinical features with other types of diabetes, leading to low diagnostic rates. In the UK, 80% of MODY patients are misdiagnosed as having type 1 or type 2 diabetes, with MODY diagnoses accounting for only 1% to 2% of all diabetes cases [1,2]. To date, 14 pathogenic genes for MODY have been identified [3,4]. Among them, MODY12 is a monogenic diabetes inherited in an autosomal dominant pattern caused by mutations in the ATP-binding cassette subfamily C member 8 (ABCC8) gene located on chromosome 11, first reported by Bowman et al. [5] in 2012. This paper presents a pedigree analysis of a suspected MODY family with ABCC8 mutations, providing clinical diagnostic evidence for the patients.

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CASE PRESENTATION

Clinical presentation

The proband, a 27-year-old male, was admitted to the Endocrinology Department of Shaoxing Central Hospital on February 20, 2024, with a chief complaint of "polydipsia, polyuria, and weight loss for 11 years, worsening for 2 years." The patient first experienced symptoms of polydipsia, polyuria, and weight loss 11 years ago but did not seek medical attention or treatment. Eight years ago, due to worsening of the aforementioned symptoms, he visited the Endocrinology Department of Shaoxing Central Hospital, where fasting blood glucose was measured at 13.27 mmol/L, glycated hemoglobin (HbA1c) was 11.1%, urinary ketones were negative, diabetes autoantibodies were negative, 24-hour urinary microalbumin was 3.5 (reference range: 2.4 - 34.3) mg/24 hours, no diabetic retinopathy was observed on fundus examination. He was initiated on Mixtard insulin + regular insulin with 4 injections for intensive glycemic control. After achieving stable blood glucose levels, the treatment was switched to Mixtard insulin 30 injections for glycemic control. After 3 months of treatment, HbA1c was rechecked at 6.1%. A steamed bun meal test showed fasting blood glucose of 7.57 mmol/L, fasting C-peptide of 2.28 (reference range: 0.3 - 3.73) ng/mL, 1-hour postprandial blood glucose of 10.31 mmol/L, 1-hour postprandial C-peptide of 3.92 ng/mL, 2-hour postprandial blood glucose of 10.28 mmol/L, 2-hours postprandial C-peptide of 5.31 ng/mL, 3-hours postprandial blood glucose of 10.30 mmol/L, and 3-hours postprandial C-peptide of 5.37 ng/mL. Throughout this period, he remained on Mixtard insulin 30 injections for glycemic control without adjustment of the regimen. Two years ago, the aforementioned symptoms worsened again. Upon outpatient reevaluation, the patient's glycated hemoglobin was 10.2%, fasting blood glucose was 10 mmol/L, and 2-hours postprandial blood glucose was 17.68 mmol/L. Insulin dosage was adjusted accordingly. Recently, the patient presented again with persistent symptoms. Upon reevaluation, fasting blood glucose was 16.91 mmol/L, glycated hemoglobin was 10.2%, urinary ketones were negative, 24-hour urinary microalbumin was 88 mg/24 hours, and fundus examination revealed retinal microaneurysms and small hemorrhages. After intensive insulin therapy with 4 injections, a steamed bun meal test was repeated, showing fasting blood glucose of 6.25 mmol/L, fasting C-peptide of 1.0 ng/mL, 1-hour postprandial blood glucose of 12.59 mmol/L, 1-hour postprandial C-peptide of 2.21 ng/mL, 2-hours postprandial blood glucose of 15.83 mmol/L, 2-hour postprandial C-peptide of 3.54 ng/mL, 3-hours postprandial blood glucose of 13.33 mmol/L, and 3-hours postprandial C-peptide of 3.2 ng/mL. Physical examination revealed a height of 172 cm, weight of 96 kg, BMI of 32.4 kg/m², blood pressure of 125/76 mmHg, with a normal body shape, no signs of Cushingoid features, and normal heart, lung, and abdominal examinations. No edema was observed in the lower extremities.

In the patient's family, both paternal grandfather and father have a history of diabetes (Figure 1). The grandfather and father were diagnosed with diabetes at around 50 and 35 years of age, respectively. They typically manage their glycemic control with oral metformin and glimepiride, achieving good glycemic control. Considering the patient's medical history and clinical features, MODY is considered as a possibility. After discussing with the patient, genetic sequencing was conducted to confirm the diagnosis. Based on the genetic diagnostic report, insulin was discontinued and treatment was switched to oral metformin, glimepiride, and liraglutide injections for glycemic control. Upon follow-up after 1 month, fasting blood glucose was retested at 5.3 mmol/L and 2-hours postprandial blood glucose was 6.7 mmol/L.

Genetic test results

With the informed consent of the patient and their family members, peripheral blood samples were collected for extraction of whole-genome DNA. Subsequently, high-throughput sequencing of whole-genome exons was performed on peripheral blood samples, and selected variant sites were validated using Sanger sequencing (performed at the Taizhou Angpao Medical Laboratory). The results revealed the presence of a heterozygous mutation c.2060C>T (p.T687M) in exon 15 of the ABCC8 gene (Chr11-174494701) in the proband, leading to the substitution of threonine with methionine at the amino acid level (Figure 2), indicating a missense mutation. According to the ACMG guidelines, this variant is classified as a variant of uncertain significance (VUS), and it has been reported as such in the ClinVar database (variant ID: 303777). This variant is found at a low frequency in normal population databases. The proband's father was found to have this variant in a heterozygous state, while the proband's mother showed no variation at this site.

DISCUSSION

MODY12 is a rare type of monogenic diabetes caused by mutations in the ABCC8 gene, inherited in an autosomal dominant pattern. Donath et al. [6] exported that diabetes caused by ABCC8 gene mutations accounts for approximately 3.2% of monogenic diabetes cases. ABCC8 is located on chromosome 11p15.1 in the ATP binding domain, encoding the sulfonylurea receptor 1 (SUR1) protein. This protein serves as a crucial subunit of the pancreatic β-cell ATP-sensitive potassium channel (KATP), participating in membrane electrical activity and regulating insulin secretion [7]. To date, 28 ABCC8 mutations associated with MODY12 have been reported, with over 150 pathogenic variants identified [8].

The polymorphism of ABCC8 gene mutations can give rise to various clinical phenotypes, including asymp-

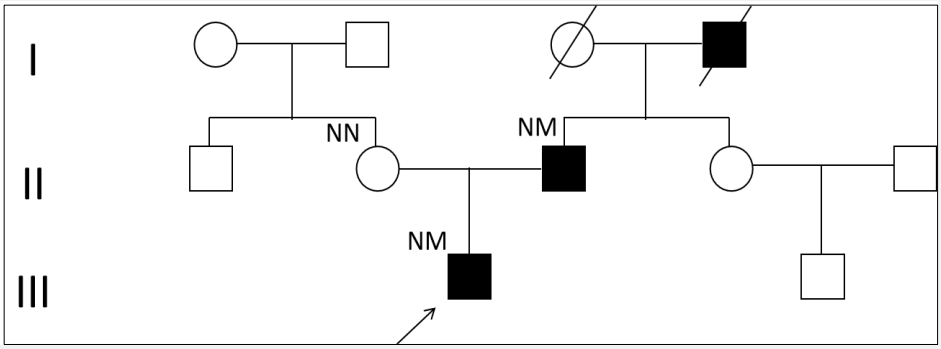

Figure 1. Pedigree of a patient with a heterozygous mutation in the ABCC8 gene (c.2060C>T; p.T687M).

The individual indicated by the black arrow is the proband. Squares represent males, circles represent females. Solid shapes represent individuals with diabetes, while hollow shapes represent individuals with normal blood sugar levels. Diagonal lines represent deceased individuals. "NN" indicates no mutation detected, while "NM" indicates detection of a heterozygous mutation.

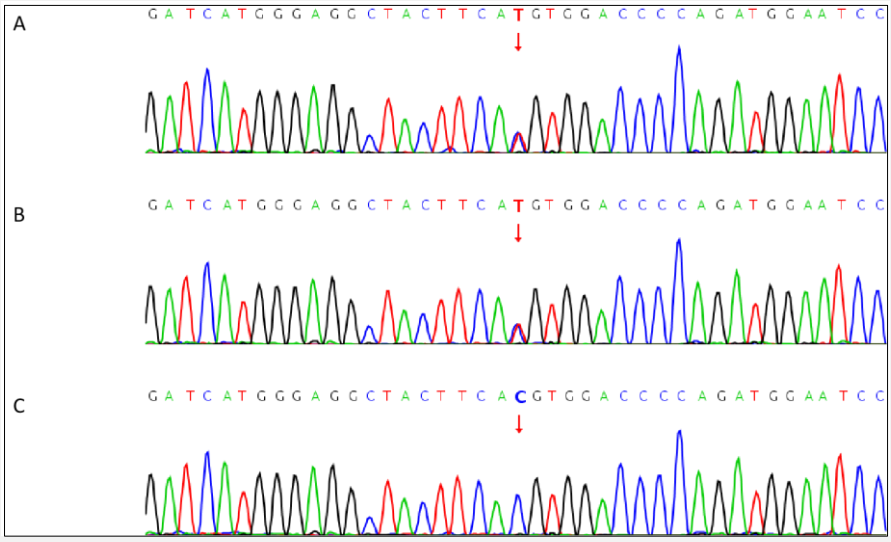

Figure 2. Sequencing chromatogram showing the heterozygous mutation (c.2060C>T; p.T687M) in exon 15 of the ABCC8 gene in this family.

A and B represent sequencing chromatograms of the proband and their father, respectively, showing the heterozygous mutation site indicated by the arrow. C depicts the sequencing chromatogram of the proband's mother, where no variation is observed at the site indicated by the arrow.

tomatic conditions, neonatal diabetes, MODY, and congenital hyperinsulinism [9]. This variability may be attributed to the type and location of mutations, as well as the interplay of other modifying genetic and environmental factors. Significant differences in age of onset, clinical presentation, and insulin dependency can exist even within the same family and mutation [10]. Shima et al. [11] reported a MODY12 pedigree where the age of onset progressively decreased and the severity of the disease worsened with each generation, highlighting the heterogeneity of diabetes within ABCC8 gene mutation families. The incidence and prognosis of complications

in MODY12 remain unclear. Insulin therapy may exacerbate proliferative retinopathy and macular edema, possibly due to increased blood glucose fluctuations induced by insulin therapy [12]. Given that sulfonylurea drugs specifically bind to the SUR1 subunit and close the channel to release insulin in an ATP-independent manner, this subtype of MODY is sensitive to sulfonylurea drug [13]. SUR1 is expressed in retinal vessels, and gliclazide has been shown to inhibit adenosine-mediated retinal vasodilation at doses as low as 5 nM [14, 15]. Therefore, sulfonylurea drugs may not only control blood sugar but also delay the progression of diabetic complications.

The patient in this case presented initially with symptoms of polydipsia, polyuria, and weight loss, without tendencies toward ketoacidosis. Diabetes autoantibodies were negative, and pancreatic function assessment revealed adequate secretion capacity. The patient was obese, leading to a tentative diagnosis of type 2 diabetes. However, onset of the disease at 16 years of age and a three-generation family history of diabetes necessitated consideration of a specific type of diabetes. Genetic testing confirmed the presence of a heterozygous missense mutation (c.2060C>T) in the ABCC8 gene, resulting in the substitution of threonine with methionine at the amino acid level. This variant has been reported as potentially benign in the ClinVar database, classified as a variant of uncertain significance. The same mutation was found in the patient's father. Additionally, the patient developed diabetic retinopathy after long-term insulin therapy. Following discontinuation of insulin and adjustment to treatment with glimepiride, metformin, and liraglutide injections, good blood sugar control was observed during the 1-month follow-up. Considering these features, MODY12 caused by ABCC8 gene mutation should be considered in this patient.

In conclusion, for patients with a high clinical suspicion of MODY, genetic testing should be performed to confirm the diagnosis. Accurate diagnosis aids in selecting appropriate treatment strategies, thereby improving prognosis for patients.

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Informed Consent:
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Declaration of Interest:
There is no conflict of interest to disclose.

References:

1. Gardner DS, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). Diabetes Metab Syndr Obes 2012;5:101-8. (PMID: 22654519)

2. 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(12):2504-8. (PMID: 20499044)

3. Prudente S, Jungtrakoon P, Marucci A, et al. Loss-of-Function Mutations in APPL1 in Familial Diabetes Mellitus. Am J Hum Genet 2015;97(1):177-85. (PMID: 26073777)

4. Firdous P, Nissar K, Ali S, et al. Genetic Testing of Maturity-Onset Diabetes of the Young Current Status and Future Perspectives. Front Endocrinol (Lausanne) 2018;9:253. (PMID: 29867778)

5. Bowman P, Flanagan SE, Edghill EL, et al. Heterozygous ABCC8 mutations are a cause of MODY. Diabetologia 2012;55 (1):123-7. (PMID: 21989597)

6. Donath X, Saint-Martin C, Dubois-Laforgue D, et al. Next-generation sequencing identifies monogenic diabetes in 16% of patients with late adolescence/adult-onset diabetes selected on a clinical basis: a cross-sectional analysis. BMC Med 2019;17(1): 132. (PMID: 31291970)

7. Patch A M, Flanagan S E, Boustred C, Hattersley AT, Ellard S. Mutations in the ABCC8 gene encoding the SUR1 subunit of the KATP channel cause transient neonatal diabetes, permanent neonatal diabetes or permanent diabetes diagnosed outside the neonatal period. Diabetes Obes Metab 2007;9 Suppl 2(Suppl 2):28-39. (PMID: 17919176)

8. Zhou Y, Sun Y, Xu C, et al. ABCC8-related maturity-onset diabetes of the young: Clinical features and genetic analysis of one case. Pediatr Diabetes 2022;23(5):588-96. (PMID: 35757975)

9. Aarthy R, Aston-Mourney K, Mikocka-Walus A, et al. Clinical features, complications and treatment of rarer forms of maturity-onset diabetes of the young (MODY) - A review. J Diabetes Complications 2021;35(1):107640. (PMID: 32763092)

10. Timmers M, Dirinck E, Lauwers P, et al. ABCC8 variants in MODY12: Review of the literature and report of a case with severe complications. Diabetes Metab Res Rev 2021;37(8):e3459. (PMID: 34014594)

11. Shima KR, Usuda R, Futatani T, et al. Heterogeneous nature of diabetes in a family with a gain-of-function mutation in the ATP-binding cassette subfamily C member 8 (ABCC8) gene. Endocr J 2018;65(10):1055-9. (PMID: 30068891)

12. Reilly F, Sanchez-Lechuga B, Clinton S, et al. Phenotype, genotype and glycaemic variability in people with activating mutations in the ABCC8 gene: response to appropriate therapy. Diabet Med 2020;37(5):876-84. (PMID: 31562829)

13. Lin L, Quan H, Chen K, Chen D, Lin D, Fang T. ABCC8-Related Maturity-Onset Diabetes of the Young (MODY12): A Report of a Chinese Family. Front Endocrinol (Lausanne) 2020;11:645. (PMID: 33013711)

14. Li Q, Puro DG. Adenosine activates ATP-sensitive K(+) currents in pericytes of rat retinal microvessels: role of A1 and A2a receptors. Brain Res 2001;907(1-2):93-9. (PMID: 11430889)

15. Jeppesen P, Aalkjaer C, Bek T. Adenosine relaxation in small retinal arterioles requires functional Na-K pumps and K(ATP) channels. Curr Eye Res 2002;25(1):23-8. (PMID: 12518240)