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CASE REPORT

De novo mutation in HNF-1β gene as a cause for Maturity-onset Diabetes of the Young type 5 with sustained hypomagnesemia

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Abstract

Background Maturity-onset Diabetes of the Young type 5 (MODY5) is clinically heterogeneous, and the genetic examination is important to provide the accurate diagnosis. Identification of more cases will better understand the genotype-phenotype correlations of this disorder.

Methods We collected the clinical and biochemical data, using the whole-exome gene detection and multiplex ligation–dependent probe Amplification to detect the pathogenic gene variants.

Results The proband is a 39-year-old female, and presenting with symptoms including polyuria, polydipsia, and weight loss for 6 months. Her BMI was 17.6 kg/m^2. Laboratory tests indicated hypokalemia (3.1 mmol/L), hypomagnesemia (0.4 mmol/L), and hypocalcemia (1.91 mmol/L). Glycated hemoglobin (HbA1c) was 13.7%, fasting C-peptide was 0.24 ng/mL (normal range: 0.3–3.73 ng/mL). Both glutamic acid decarboxylase and islet cell antibodies were negative. Abdominal magnetic resonance image showed the agenesis of the tail and body of the pancreas and the presence of disseminated cysts of the left kidney. Genetic examination displayed a de novo heterozygous deletion of the whole HNF-1B gene (NM_000458.3). Three-year follow-up after the diagnosis showed that the patient has sustained hypomagnesemia and cannot maintain an appreciable increase in serum magnesium levels (0.52–0.61 mmol/L), although she was using the double-dose magnesium aspartate. Moreover, she cannot achieve good glucose control either.

Conclusion Our findings indicted that MODY is highly heterogeneous and patients with additional extrapancreatic clinical features and hypomagnesemia should be screened for MODY5.

Keywords Maturity-onset Diabetes of the Young · Hypomagnesemia · Hepatocyte nuclear factor-1βeta (HNF-1β) · Mutation · Diabetes mellitus

Introduction

Maturity-onset Diabetes of the Young (MODY) is a rare group of dominantly inherited and clinically heterogeneous diabetes mellitus [1]. MODY type 5 (MODY5) accounts for 2–6% of MODY diagnoses, whose typical characterization is relatively worse beta cell function and additional extrapancreatic clinical features, like liver dysfunction, renal disease, and genital malformation [2]. This disorder is caused by mutations of the hepatocyte nuclear factor-1beta (*HNF1β*) gene. *HNF1β* is an important transcription factor in the development of the pancreas, kidney, liver, and genital tract [3]. *HNF1β* gene located on chromosome 17q12 and more than 100 different mutations in this gene have been identified since it was associated with MODY5 in 1997 [1, 4].

Stiles et al. reported *HNF1β* deletion as a cause for a patient with chronic, treatment-resistant hypomagnesemia, but without diabetes mellitus (DM) [5]. In this report, we described a rare heterozygous whole-gene deletion in *HNF1β* gene that was identified in a proband with MODY5 and sustained hypomagnesemia.

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Methods

Ethics

This study was approved by the ethics institutional review board of the Laiwu Central Hospital of Xinwen Mining Group. Written informed consents were obtained from the proband and her parents.

Case presentation

Clinical features

The proband is a 39-year-old Chinese female without a prior documented remarkable medical history. She presented with symptoms including polyuria, polydipsia, and weight loss for 6 months. Hyperglycemia (fasting plasma glucose ranges from 8.3 to 13.6 mmol/L and 2-h postprandial glucose was over 20 mmol/L) and ketosis but without metabolic acidosis were identified at presentation. She was diagnosed as type 2 DM and treated with insulin in another hospital. Due to poorly controlled blood glucose, she was admitted to our hospital. Further investigation revealed that she (1) was a premature infant, (2) was feeling fatigue from a young age, (3) had suffered from paroxysmal extremities numbness and spontaneous hand tremor for several years, and (4) was aborted at 6-month gestation for unknown reasons.

Her BMI was 17.6 kg/m^2. A physical examination revealed no obvious abnormalities. Laboratory tests indicated hypokalemia (3.1 mmol/L), hypomagnesemia (0.4 mmol/L), and hypocalcemia (1.91 mmol/L). Fasting plasma glucose was 7.6 mmol/L and 2-h postprandial glucose 19.3 mmol/L. Glycated hemoglobin (HbA1c) was 13.7% determined using high-performance liquid chromatography (HPLC) with the Hemoglobin A1c analyzer (TOSOH Corporation, Japan). Used an automatic biochemistry analyzer (Beckman Coulter Analyzer AU58 Series, USA) to analyze the following parameters. Fasting C-peptide was 0.24 ng/mL (normal range: 0.3–3.73 ng/mL), 1-h and 2-h postprandial C-peptides were 0.44 and 0.15 ng/mL, respectively. Levels of serum ALT, AST, BUN, and creatinine were normal. Both glutamic acid decarboxylase and islet cell antibodies were negative.

Abdominal magnetic resonance image showed the agenesis of the tail and body of the pancreas and the presence of disseminated cysts of the kidney (Fig. 1).

The genetic analysis

Genetic tests were carried out on the patient and her parents 2 years later after the diagnosis of DM. Genomic DNA was isolated from peripheral blood leukocytes using QIAamp DNA Mini Kit (Qiagen, Germany) following the manufacturer's instructions. Whole-exome sequencing (WES) was performed using SeqCap EZ Med Exome Enrichment Kit (Roche NimbleGen, USA) and the Illumina HiSeq sequencing platform. Genetic examination by the WES and multiplex ligation–dependent probe amplification (MLPA) detected a 1.26-Mbp heterozygous deletion (Chr17:34842450-36105089) that includes *HNF1β* gene (NM_000458.3, Fig. 2). It was proved to be a de novo mutation because neither her parents shared the deletion. Therefore, our patient was genetically confirmed MODY5.

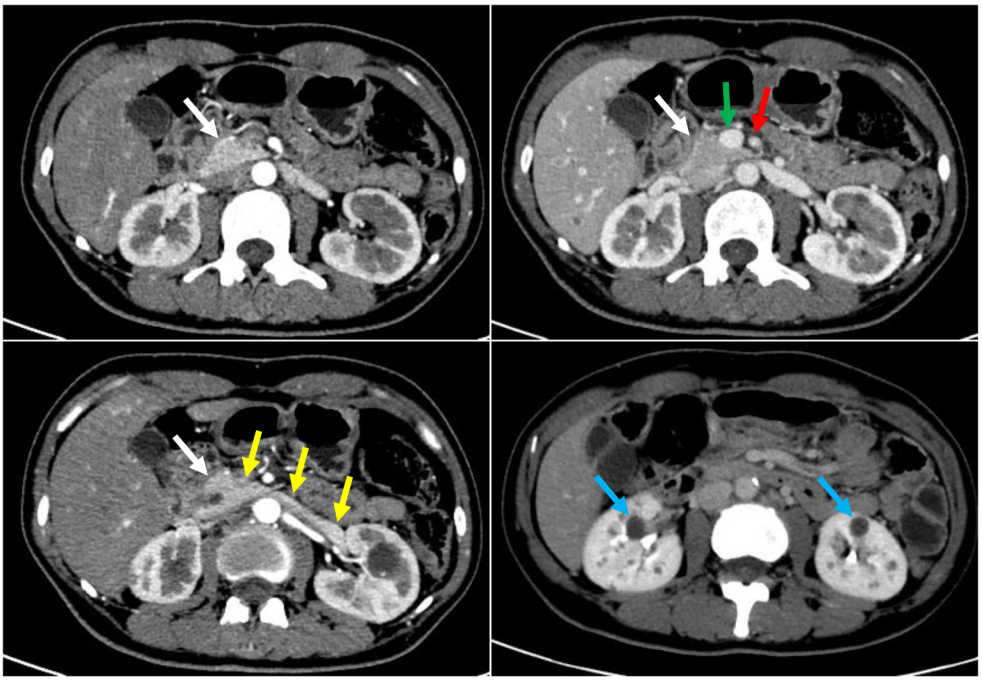

Fig. 1 Abdominal magnetic resonance image showed the agenesis of the tail and body of the pancreas and the presence of disseminated cysts of the kidney. Arrow in white, the pancreatic uncinate process. Arrow in green, superior mesenteric vein. Arrow in red, superior mesenteric artery. Arrow in yellow, body and tail of pancreas. Arrow in blue, disseminated cysts of the kidney

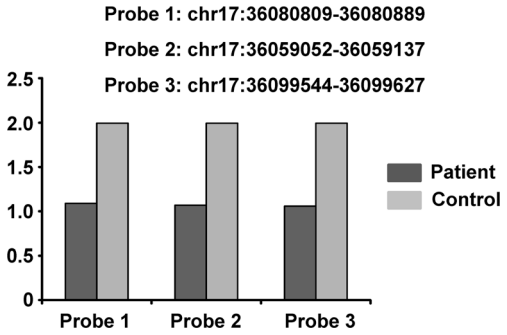

Fig. 2 Genetic examination by multiplex ligation–dependent probe amplification (MLPA) displayed a heterozygous deletion of the whole *HNF1β* gene (NM_000458.3)

In addition, the WES revealed two heterozygous missense variants in *PPP1R3A* (NM_002711 c.1465T>A, p.F489I) and *PLIN1* (NM_002666, c.929A>G, p.E310G) genes, respectively (Fig. 3). The variation c.1465T>A in *PPP1R3A* gene results in a change in the 489th amino acid of the encoded protein from F to I. The variation c.929A>G in *PLIN1* gene results in a change in the 310th amino acid of the encoded protein from E to G. Neither of the variations was reported in the database of the Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/) or the Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/). Both the patient and her mother carried these two mutations; however, her mother had no diabetes and hypomagnesemia. Therefore, these are likely to be variations with unknown significance and benign.

Follow-up

Serum magnesium was 0.4 mmol/L (normal range: 0.7–1.0 mmol/L) at presentation to our department and dropped to 0.31 mmol/L, despite the oral replacement therapy (magnesium 395.7 mg daily) for 7 days. Later, this dose was doubled for a trial period, with a slight increase in serum magnesium (0.46 mmol/L). Since then, the patient is using the double-dose magnesium aspartate. However, she could not maintain an appreciable increase in serum magnesium levels (0.52–0.61 mmol/L) and achieve reduction of her symptoms.

Three-year follow-up after the diagnosis of DM showed that the patient could not achieve good glucose control although by intensified insulin therapy (insulin glargine and insulin lispro). HbA1c was 8–9%.

Discussion

We herein reported a heterozygous deletion of the whole *HNF1β* gene in a Chinese patient with the phenotypes of MODY5 and sustained hypomagnesemia.

Due to relatively poor beta cell function and progressive hyperglycemia, patients with MODY5 usually required an intensive insulin treatment. Notably, MODY5 encompasses a wide extrapancreatic clinical spectrum [1, 6]. Renal disease, especially the presence of renal cysts, is the most frequently detected feature. Other features include pancreatic atrophy, exocrine pancreatic dysfunction, liver dysfunction, genital tract malformation, and early-onset gout [7, 8]. Analysis for mutations of *HNF1β* is recommended in young diabetic patients particularly when pancreatic atrophy, kidney, or genital abnormalities are present.

A whole *HNF1β* gene deletion is the most common mutation, occurring in half of patients with MODY5. Because the *HNF1β* gene located on chromosome 17q12 in humans, the *HNF1β* deletion has recently been regarded to be linked with the 17q12 deletion syndrome in all cases [9]. The 17q12 deletion syndrome is an extremely rare microdeletion syndrome whose estimated prevalence is 1.6 per 100.000 people. The penetrance of this disorder is high, but its expressivity is variable [10]. The 17q12 deletion syndrome can either be inherited from an affected parent in an autosomal dominant

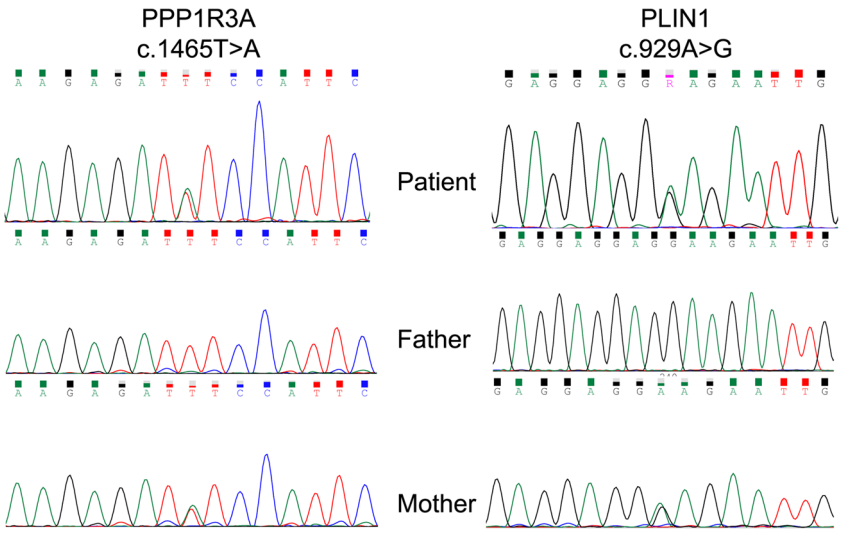

Fig. 3 Whole-exome sequencing (WES) revealed two heterozygous missense mutation in PPP1R3A (NM_002711 c.1465T>A, p.F489I) and PLIN1 (NM_002666, c.929A>G, p.E310G) gene, respectively

manner or occur de novo. Actually, the deletion mutation in 70% of the cases is de novo [11]. Thus, presence of DM and typical clinical features in our patient indicates 17q12 deletion syndrome as possible diagnosis. The patient in this case required insulin treatment because of impaired insulin secretion accompanied by pancreatic atrophy. She had renal cysts and hypomagnesemia. Based on the above findings, her phenotype was compatible with MODY5.

Hypomagnesemia has been associated with disorders resulting from mutations in the *HNF1β* gene [2]. The occurrence of hypomagnesemia is described with various types of *HNF1β* mutations [6, 12, 13]. It is believed to occur through magnesium wasting in the renal distal convoluted tubule. Stiles et al. reported a 29-year-old female patient who suffered from an unexplained hypomagnesemia for 8 years, but without DM. Genetic analysis showed that this disorder was also caused by a heterozygote 1.5-Mb deletion on chromosome 17q12 encompassing *HNF1β* gene [5]. It was noted that our patient developed DM at about 39-year old, though MODY5 generally occurred before the age of 30 years. Therefore, the patient reported by Stiles et al. should be followed up regularly on her glycemic state to detect DM earlier.

In summary, features caused by *HNF1β* deletion are highly heterogeneous amongst patients and genotype/phenotype correlation is still unclear up to now. *HNF1β* mutations can be part of the 17q12 deletion syndrome which are one of the most common causes of MODY5 characterized by congenital anomalies of the pancreas and kidney. Sustained and treatment-resistant hypomagnesemia are also associated with the *HNF1β* mutation.

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Author contributions Y.Z. conceived of and supervised the project, and revised the manuscript content. B.R. and Y.C. collected and analyzed the data, and drafted the manuscript. S.Z., Q.Z., J.W., and S.C. took responsibility for the integrity of the data analysis. All the authors have read and approved the final submitted version.

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Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate This study was approved by the ethics institutional review board of the Laiwu Central Hospital of Xinwen Mining Group. Prior to sample collection, written informed consent was obtained from the proband and her parents.

Patient consent for publication All subjects provided consent for publication.

Code availability Not applicable.

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