



Hepatocyte nuclear factor 1B deletion, but not intragenic mutation, might be more susceptible to hypomagnesemia

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Keywords

Hepatocyte nuclear factor 1B, Hypomagnesemia, Maturity-onset diabetes of the young

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ABSTRACT

Aims: *HNF1B* syndrome is caused by defects in the hepatocyte nuclear factor 1B (*HNF1B*) gene, which leads to maturity-onset diabetes of the young type 5 and congenital organ malformations. This study aimed to identify a gene defect in a patient presenting with diabetes and severe diarrhea, while also analyzing the prevalence of hypomagnesemia and its correlation with the *HNF1B* genotype.

Materials and Methods: Whole exome sequencing was used to identify responsible point mutations and small indels in the proband and their family members. Multiplex ligation-dependent probe amplification was carried out to identify *HNF1B* deletions. Furthermore, an analysis of published data on 539 cumulative *HNF1B* cases, from 29 literature sources, was carried out to determine the correlation between the *HNF1B* genotype and the phenotype of serum magnesium status.

Results: Using multiplex ligation-dependent probe amplification, we identified a de novo heterozygous *HNF1B* deletion in the patient, who showed dorsal pancreas agenesis and multiple kidney cysts, as detected by magnetic resonance imaging. Magnesium supplementation effectively alleviated the symptoms of diarrhea. Hypomagnesemia was highly prevalent in 192 out of 354 (54.2%) patients with *HNF1B* syndrome. Compared with patients with intragenic mutations, those with *HNF1B* deletions were more likely to suffer from hypomagnesemia, with an odds ratio of 3.1 (95% confidence interval 1.8–5.4).

Conclusions: Hypomagnesemia is highly prevalent in individuals with *HNF1B* syndrome, and those with *HNF1B* deletion are more susceptible to developing hypomagnesemia compared with those with intragenic mutations. The genotype–phenotype associations in *HNF1B* syndrome have significant implications for endocrinologists in terms of genotype detection, treatment decisions and prognosis assessment.

INTRODUCTION

Hepatocyte nuclear factor 1B (*HNF1B*), also known as transcription factor 2 (*TCF2*), plays an important role in organ specification from endoderm and mesoderm during

embryogenesis^{1,2}. Molecular defects of *HNF1B* are associated with a variety of congenital organ abnormalities, including pancreatic agenesis, kidney malformation, liver abnormalities, genital tract anomalies and maturity-onset diabetes of the young 5 (*MODY5*)³. Additionally, affected patients might show abnormal biological variables, such as impaired renal function^{3–5}, electrolyte disturbance⁶, hyperuricemia early-onset gout⁶,

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deranged liver function tests^{3,4} and exocrine pancreatic dysfunction⁷. The disease caused by the molecular defects in *HNF1B* was called *HNF1B* syndrome³.

To date, a total of 377 different *HNF1B* molecular defects have been identified, consisting of gross deletions (21%), mis-sense or nonsense mutations (50%), small deletions (15%) and splice-site mutations (6%). Patients with *HNF1B* deletions are usually found to have a 17q12 deletion spanning 15 genes⁸.

The phenotypes of *HNF1B* syndrome are remarkably heterogeneous³. In patients with *HNF1B* syndrome, diabetes is often the initial clinical manifestation, which is actually a form of monogenic diabetes known as MODY5. MODY (monogenic diabetes) is a rare autosomal dominant subtype of diabetes and accounts for 1–3% of diabetes diagnoses^{9,10}. The most common MODY subtype is *HNF1A*-MODY3 (58%), whereas MODY5 only accounts for 2–6% of MODY diagnoses^{10,11}. A study showed that the frequency of Japanese MODY1-3, 5 and 6 were 7.6%, 36.3%, 39.4%, 13.6% and 3.0%, respectively¹². However, the prevalence of MODY5 might be underestimated due to its wide phenotypical variability. Along with the increasing awareness of endocrinologists¹³, progressive genetic testing methods and the emergence of the MODY clinical risk calculator¹⁴, many more monogenic diabetes cases would be efficiently diagnosed. Nowadays, the clinical characteristics, treatment and complications of MODY are better understood, including both the common (MODY1-3, 5) and rarer (MODY4, 6–14) subtypes of MODY¹⁵.

Here, we reported a case with a heterozygous whole *HNF1B* gene deletion, which rarely manifested as diabetes combined with severe diarrhea. The diarrhea in this patient significantly eased when the hypomagnesemia was rectified. Furthermore, we carried out an analysis to investigate the prevalence of hypomagnesemia in individuals with *HNF1B* syndrome, and assessed genotype–phenotype correlations between hypomagnesemia and *HNF1B* genotype.

MATERIALS AND METHODS

Case presentation

A 33-year-old male patient presented to the Department of Metabolism & Endocrinology at the Second Xiangya Hospital, Central South University, Changsha, Hunan, China, with symptoms of diabetes, weight loss and severe diarrhea. He had a normal body stature (body mass index 23.1 kg/m²) before becoming sick, and had been showing symptoms of polyuria, polydipsia and polyphagia for over a year before seeking treatment. Due to worsening symptoms, he began to experience lower limb pain and numbness and was subsequently diagnosed with type 2 diabetes and diabetic neuropathy, for which he received insulin therapy. Then, he developed severe diarrhea, resulting in weight loss of 15 kg (body mass index 17.4 kg/m²) and the onset of a cachectic state (Figure 1a). Negative stool and blood cultures helped to exclude infectious enteritis and disease. Laboratory examinations showed impaired islet

function, amylase deficiency, abnormal liver function, decreased renal function and hypomagnesemia (Table 1). The patient tested negative for islet autoantibodies (glutamic acid decarboxylase autoantibodies, insulinoma-2 associated autoantibodies and zinc transporter-8 autoantibodies) and had no family history of diabetes in the first degree. Magnetic resonance showed pancreatic hypoplasia and small cysts in bilateral kidneys, with a paucity of the distal major pancreatic duct shown by magnetic resonance cholangiopancreatography, as shown in Figure 1b–d.

Given the multiorgan dysfunction and genetic factors, genetic testing was recommended for the patient and his family members, with written informed consent. All procedures were in accordance with the principles of the Declaration of Helsinki, and were approved by the Human Ethics Committee of the Second Xiangya Hospital of Central South University (No. 2019-Research-40).

Molecular genetic testing

Peripheral venous blood was collected from the proband, his younger sister and his parents. Deoxyribonucleic acid was extracted using Qiagen FlexiGene DNA Kit (Cat. 512206; Qiagen, Hilden, Germany) according to the protocol. Whole exome sequencing was used to identify responsible point mutations and small indels. The genomic deoxyribonucleic acid was randomly sheared into 180–280 bp fragments, which were amplified by polymerase chain reaction and sequenced by the Illumina HiSeq X Ten platform. Meanwhile, multiplex ligation-dependent probe amplification was undertaken to identify the exon deletion of the MODY gene. The multiplex ligation-dependent probe amplification kit (Cat. P241; MRC-Holland, Amsterdam, the Netherlands) was designed to detect copy number variations in the *HNF1B*, *GCK*, *HNF1A* and *HNF4A* genes.

Literature search and data extraction

Literature search, study selection and data extraction were carried out independently by two investigators (Wang and Lin). A systematic search was carried out in PubMed for the published literature up to March 2022, with the terms *HNF1B*, *TCF2*, diabetes mellitus type MODY5 and 17q12 deletion. In total, 539 published cases with genetically verified *HNF1B* defects were assessed, and 354 of them were with serum magnesium status (Table 2). Hypomagnesemia is defined as serum magnesium <0.7 mmol/L or lower than the lower limit of reference value in each publication^{6,16}. Finally, data from 227 cases with both serum magnesium and *HNF1B* genotype were extracted and pooled for phenotype–genotype analysis.

RESULTS

Genetic study result

As the present patient was rather young and did not present with metabolic syndrome, the diagnosis of type 2 diabetes was

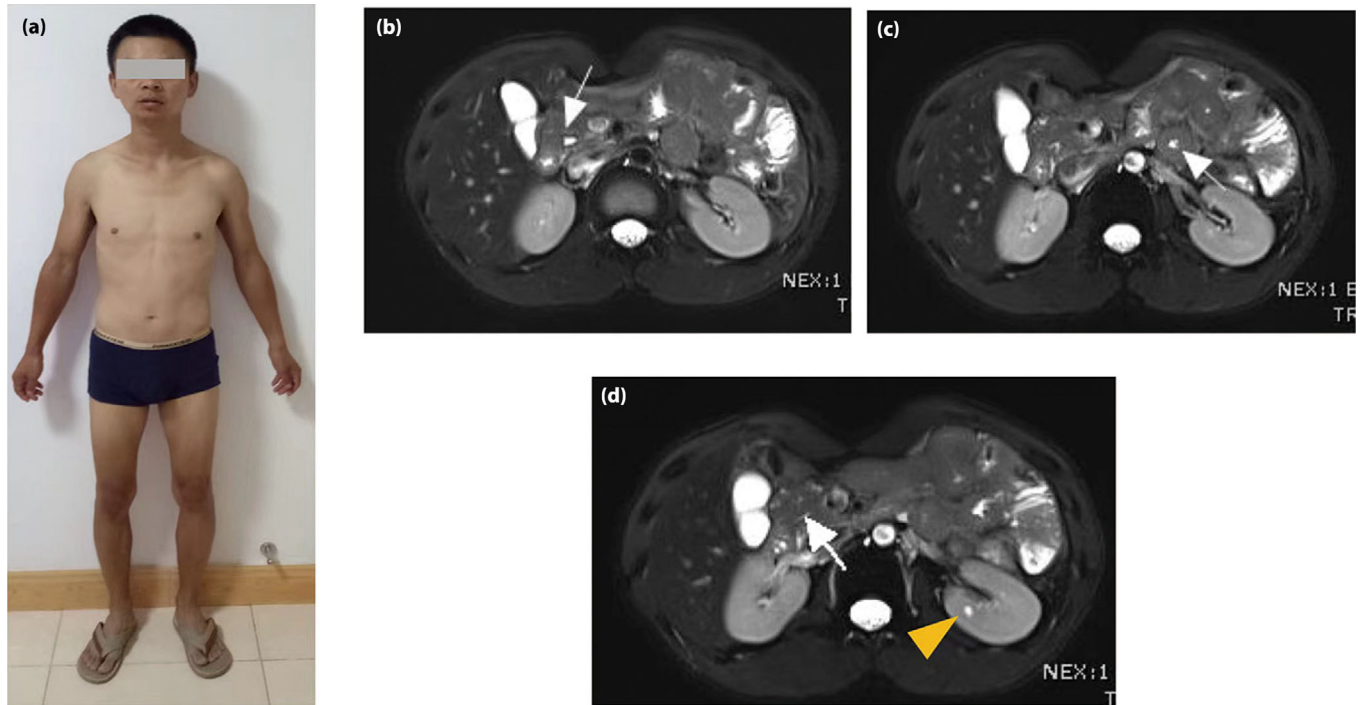


Figure 1 | Images of the hepatocyte nuclear factor 1B deletion patient, and his magnetic resonance showing typical malformation of the visceral organs. (a) The patient showed a thin figure, but without facial and trunk dysmorphic features. (b) The pancreatic head (white arrow) was present, whereas the pancreatic body and tail was absent in the scan. (c) The pancreatic body and tail were not visible on serial slices, and the intestine tissue (white arrow) was present in the expected location of the distal pancreas. (d) Magnetic resonance cholangiopancreatography showed the short main pancreatic duct (white arrow) and small cysts in the kidney (yellow triangle).

Table 1 | Laboratory examinations of the patient with *HNF1B* syndrome

Parameter	First admission	Follow up At 4 months later	Reference interval
0 min glycemia (mmol/L)	5.53	7.77	3.9–6.1
120 min glycemia (mmol/L)	7.82	9.12	<7.8
0 min C-peptide (pmol/L)	279.7	291.3	223–746
120 min C-peptide (pmol/L)	465.7	777.1	-
HbA1c (%)	5.1	6.0	3.9–6.1
Amylopsin (U/L)	15.6 ↓	14.6 ↓	17–115
ALT (U/L)	116.3 ↑	41.4	9–55
AST (U/L)	56.2 ↑	37.6	15–40
ALP (U/L)	153.2 ↑	105.6	45–125
Potassium (mmol/L)	4.14	3.44 ↓	3.5–5.5
Calcium (mmol/L)	2.42	2.22	2.11–2.52
Phosphate (mmol/L)	1.12	1.1	0.85–1.51
Cr (μmol/L)	102.3 ↑	89.2	44–92
Magnesium (mmol/L)	0.59 ↓	0.75 ↓	0.85–1.51

ALP, alkaline phosphatase; ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; Cr, creatinine; HbA1c, hemoglobin A1c.

doubtful. Therefore, the etiology of his diabetes remained unclear. Whole exome sequencing was used to search for gene mutations responsible for the patient’s multiorgan dysfunction, but no such mutations were found. However, copy number variation analysis using CODEX and XHMM software showed a predicted segment deletion spanning nearly the entire *HNF1B* gene. Therefore, successive multiplex ligation-dependent probe amplification was carried out to identify the *MODY* gene deletion in the proband and his family members, which confirmed a *de novo* heterozygous whole *HNF1B* deletion in the proband (Figure 2b–e).

Diagnosis and treatment

As a result, the diagnosis of this patient was *HNF1B* syndrome, and the diabetes type was *MODY5*, not type 2 diabetes. The patient’s severe and refractory diarrhea was likely attributed to a combination of digestive enzyme deficiency, diabetic autonomic neuropathy and hypomagnesemia that increased intestinal peristalsis. The treatment plan involved insulin aspart 30, digestive enzyme capsules, neurotrophic drugs and oral magnesium supplements. At the 4-month follow up, hypomagnesemia persisted; however, there was a remarkable improvement in serum magnesium levels (Table 1). Furthermore, diarrhea was significantly alleviated, with well-formed bowel movements and

a reduced frequency of two or three times per day. The patient was well managed in terms of blood glucose control (hemoglobin A1c 6.0%) and experienced a weight gain of 6 kg. After being discharged for 1 year, the patient ceased taking the digestive enzyme capsules and neurotrophic drugs. However, diarrhea remained well controlled with the use of magnesium supplements.

Genotype–phenotype correlations

Persistent hypomagnesemia and refractory diarrhea were observed in the *HNF1B* case. However, no previous systematic study has focused on hypomagnesemia in the *HNF1B* genotype. Therefore, our aim was to determine the genotype–phenotype correlations related to hypomagnesemia in *HNF1B* syndrome.

After carrying out a PubMed search and independent review by two investigators, a total of 30 publications were included in the present study. Finally, a total of 354 cases with serum magnesium status were extracted from 539 cases in 29 publications. The frequency of hypomagnesemia was 54.2% (192/354 cases). Among the 227 cases with both *HNF1B* genotype and serum magnesium status individually (Table S1), the χ^2 -test showed that hypomagnesemia was more frequently present in patients with *HNF1B* deletion than in those with intragenic mutations (61.8 vs 34.1%, $P < 0.001$; Table 3). More specifically, patients with *HNF1B* deletions were more prone to suffering from hypomagnesemia than those with intragenic mutations, with an odds ratio of 3.1 (95% confidence interval 1.8–5.4). Next, we aimed to classify the genotypes into *HNF1B* deletion, missense mutation, nonsense mutation and splice-site mutation for subsequent analysis. Ultimately, the corresponding genotypes were extracted from 202 cases (Table S2). The χ^2 -test showed statistical differences in magnesium ion status among *HNF1B* deletion, missense mutation, nonsense mutation and splice-site mutation (Table S3). Furthermore, patients with *HNF1B* deletions were more likely to have hypomagnesemia than those with *HNF1B* missense mutations, with an odds ratio of 5.2 (95% confidence interval 2.3–11.4). Subsequently, we also extracted the corresponding magnesium ion concentrations from 65 patients and found that diagnosing *HNF1B* deletion or intragenic mutation based on serum magnesium concentration yielded an area under the curve of 0.74 (Youden index 0.4, cut-off value 1.6 mg/dL, sensitivity 61.1%, specificity 83.0%; Figure 3).

DISCUSSION

The results of the present study showed that hypomagnesemia is very common in *HNF1B* syndrome, especially in patients with a whole *HNF1B* deletion. The various manifestations in *HNF1B* syndrome can be attributable to the fact that *HNF1B* acts as a promiscuous transcription factor, regulating over 25 genes in multiple systems¹⁷. In the present study, a case with a heterozygous whole *HNF1B* deletion was genetically diagnosed with manifestations including HNF1B-MODY (MODY5), exocrine pancreatic dysfunction, dorsal pancreatic

agenesis and extrapancreas phenotypes consisting of abnormal liver test, hypomagnesemia, reduced estimated glomerular filtration rate and renal cysts. The accurate diagnosis is of great benefit for the treatment, and would be great help for antenatal genetic counseling for this patient and others with genetic diabetes.

There have been nearly 20 genes associated with inherited hypomagnesemia, which can be classified into four groups: hypercalciuric hypomagnesemia, Gitelman-like hypomagnesemia, mitochondrial hypomagnesemia and other hypomagnesemia¹⁸. Combined with clinical manifestations, a differential diagnosis strategy in a flowchart has been established for inherited hypomagnesemia¹⁹. Hypomagnesemia was first reported to be associated with *HNF1B* syndrome in 2009²⁰. It was found that 44% (8/18) of *HNF1B* patients had hypomagnesemia versus 2% (1/48) of patients with renal malformations, but without *HNF1B* defects. Analogously, but in a larger group, we showed that hypomagnesemia was present in 54.2% (192/354) of patients with *HNF1B* syndrome. Given the high prevalence of hypomagnesemia in *HNF1B* defects, hypomagnesemia is one of the sensitive features that show *HNF1B* defects. Consequently, hypomagnesemia, along with diabetes and morphological abnormalities of the kidney and other organs, has been weighted to create the *HNF1B* score for selecting patients for *HNF1B* genetic screening^{6,21}.

Previous studies have shown that serum magnesium levels were lower in the deletion group¹⁶. Nevertheless, they found no difference in magnesium status between patients with *HNF1B* intragenic mutations and deletions^{16,20,22}. In the present study, we showed that patients with *HNF1B* deletion were more likely to suffer from hypomagnesemia than those with intragenic mutation by a large sample size. The contradiction might be due to the fact that the frequency of hypomagnesemia increased with age in pediatric patients²², and became obviously discriminatory in the adult population, but not in the pediatric cohort²¹. Therefore, previous studies with only samples of children or small sample sizes have drawn divergent conclusions. Therefore, a genotype–phenotype correlation exists between *HNF1B* and hypomagnesemia, to the endocrinologists. Hypomagnesemia has a high positive predictive value for *HNF1B* deletion, especially in adult patients.

HNF1B defects lead to the transcriptional inactivation of *FXRD2*²³, a gene that encodes the γ subunit of the Na^+/K^+ -ATPase, which mediates the reabsorption of magnesium in the distal convoluted tubule^{20,24}. Therefore, *HNF1B* mutation results in hypomagnesemia due to renal wasting^{3,20,25}. HNF-1 α and HNF-1 β are homeoproteins, and have been found to form heterodimers both *in vitro* and *in vivo* over the past 30 years^{26–28}. HNF-1 β and HNF-1 α are sequentially expressed and committed to the renal tubular differentiation during embryogenesis^{26,28}. Meanwhile, patients with MODY3 (*HNF1A* mutation) have also been observed with kidney malformations²⁹. A previous study showed that the epithelia of distal convoluted tubule expressed HNF-1 α , as well as HNF-

Table 2 | Published studies reported HNF1B cases with serum magnesium status

No.	Year published	First author	Hypomagnesemia (n)	Normomagnesemia (n)	Cases with magnesium data (n)	Frequency of hypomagnesemia (%)	Total HNF1B cases (n)	Country	Details of each study
1	2009	Adalat ²⁰	8	10	18	44.4	21	UK	Screened out 21 HNF1B cases from 91 patients with RM
2	2011	Faguer ²⁵	10	6	16	62.5	27	France	Focused on HNF1B nephropathy in 27 cases
3	2012	Roelandt ³³	3	0	3	100.0	3	Belgium	Liver biopsy of 3 HNF1B cases
4	2012	Faguer ³⁴	4	7	11	36.4	11	France	Studied the expression of renal cystic genes in 11 HNF1B cases
5	2013	Ferrè ³⁵	8	3	11	72.7	11	The Netherlands	Reported 11 HNF1B cases with early hyperparathyroidism
6	2015	van der Made ³⁰	3	0	3	100.0	3	France	Hypomagnesemia in 3 HNF1B cases
7	2015	Raaijmakers ³⁶	5	15	20	25.0	20	Belgium	Screened out 20 HNF1B cases from 205 patients with CAKUT
8	2016	Gondra ³⁷	1	4	5	20.0	7	France	Reported 7 HNF1B fetuses presenting with hyperchogenic kidneys
9	2016	Dotto ³⁸	1	0	1	100.0	1	Brazil	Reported an HNF1B case suffered DKA and died of renal failure and sepsis
10	2016	Clissold ¹⁶	18	16	34	52.9	38	UK	Kidney disease and psychiatric disorder in 38 HNF1B cases
11	2016	Verhave ¹⁷	3	2	5	60.0	5	The Netherlands	Reported 5 HNF1B cases
12	2016	Bech ³⁹	5	0	5	100.0	5	The Netherlands	Reported 5 HNF1B cases with hypomagnesemia
13	2017	Wang ⁴⁰	0	2	2	0.0	2	China	Reported 2 HNF1B cases
14	2017	Kettunen ⁴¹	10	2	12	83.3	14	Finland	Enrolled 14 HNF1B cases to study biliary anomalies
15	2017	Dubois-Laforque ³	49	16	65	75.4	201	France	Included 201 HNF1B cases for genotype-phenotype study
16	2017	Carrillo ⁴²	1	0	1	100.0	1	Spain	Reported a case with good response to oral therapy
17	2017	Horinouchi ¹⁹	1	0	1	100.0	1	Japan	Reported 1 HNF1B case
18	2018	Raman ⁴³	1	0	1	100.0	1	America	Reported 1 HNF1B case
19	2018	Stiles ³²	1	0	1	100.0	1	UK	Reported 1 HNF1B case
20	2019	Madariaga ⁴⁴	9	8	17	52.9	23	Spain	Screened out 23 HNF1B cases from 60 suspected patients
21	2019	Omura ⁴⁵	1	0	1	100.0	1	Japan	Reported 1 HNF1B case
22	2019	Nagano ⁴⁶	13	18	31	41.9	33	Japan	Screened out 33 HNF1B cases from 596 suspected patients
23	2019	Dotto ⁴⁷	3	2	5	60.0	5	Brazil	Reported 2 HNF1B pedigrees

Table 2. (Continued)

No.	Year published	First author	Hypomagnesemia (n)	Normomagnesemia (n)	Cases with magnesium data (n)	Frequency of hypomagnesemia (%)	Total <i>HNF1B</i> cases (n)	Country	Details of each study
24	2019	Okorn ⁴⁸	12	38	50	24.0	62	Germany	Recruited 62 children with <i>HNF1B</i> nephropathy
25	2019	Pinon ⁴⁹	1	3	4	25.0	4	Italy	Reported 4 <i>HNF1B</i> cases presenting with neonatal cholestasis
26	2019	Al-Khawaga ⁵⁰	1	0	1	100.0	1	Qatar	Reported 1 <i>HNF1B</i> case
27	2019	Adalat ²²	23	19	42	54.8	52	UK	Screened out 52 <i>HNF1B</i> cases from 199 pediatric patients with RM
28	2019	Li ⁵¹	1	0	1	100.0	1	USA	Reported 1 <i>HNF1B</i> case
29	2021	Motyka ⁵²	3	1	4	75.0	4	Poland	Reported 4 <i>HNF1B</i> cases
30	2021	Patouni ⁵³	1	0	1	100.0	1	Greece	Reported 1 <i>HNF1B</i> case
		In total	192	162	354	54.2	539		

CAKUT, congenital abnormalities of kidney and urinary tract; *HNF1B*, hepatocyte nuclear factor 1B; RM, renal malformations.

1 β ²⁰. Hence, HNF-1 β probably binds to HNF-1 α to form heterodimers in the distal convoluted tubule to regulate the magnesium absorption, which indicates that haploinsufficiency is the preponderant mechanism for hypomagnesemia in patients with *HNF1B* deletion. Thus, our hypothesis about this genotype–phenotype correlation in hypomagnesemia might be that haploinsufficiency of *HNF1B* allele deletion insufficiently activates the *FXYD2* transcription and leads to decreased absorption of magnesium in the renal. In contrast, there might be some relationships between the other genes on chromosome 17q12 and hypomagnesemia.

As *HNF1B* syndrome is a multiorgan disease, individualized treatment should be developed for patients according to the organs affected. The clinical features of hypomagnesemia caused by *HNF1B* syndrome range from asymptomatic to fatigue, tetany, seizures, cardiac arrhythmias and even death^{18,30}. Diarrhea was rarely reported in *HNF1B* syndrome. Physiologically, magnesium inhibits the sensitivity of acetylcholine receptors on the endplate membrane. During hypomagnesemia, the repressive effect on the smooth muscle of digestive tract is relieved, which enhances intestinal motility and causes diarrhea in patients³¹. As previously mentioned, the lack of digestive enzyme due to exocrine pancreatic dysfunction was another factor for diarrhea in *HNF1B* patients.

The glycemia in the present patient was well controlled with insulin administration. However, the refractory diarrhea was not cured after receiving neurotrophic drugs and loperamide. With the accurate genetic diagnosis, it has raised our attention that besides diabetic autonomic neuropathy, deficiencies in digestive enzymes and hypomagnesemia were also major causes of the severe diarrhea. Therefore, compound digestive enzymes (dietary advanced glycation end-products) and magnesium salts were added to this patient's treatment. Other treatments for *HNF1B* syndrome include protecting the liver, relieving jaundice, lowering uric acid levels and maintaining electrolyte balance, depending on the systems affected.

The present study had several limitations. First, the sample size included in the study was relatively small, and future studies with larger prospective designs are needed to establish causal relationships. Second, only English-language studies were included, which might introduce bias due to the lack of literature in other languages. Third, many of the collected samples lacked specific subtyping of mutation types and serum magnesium concentrations, potentially limiting the clinical significance. Finally, the present study focused on investigating the impact of *HNF1B* mutations on hypomagnesemia, without extensively analyzing the effects of other genes within the deleted segment. Further research is needed to explore the potential impact of these genes in more detail.

In summary, the present study identified a case of MODY5 with a heterozygous *HNF1B* deletion. Furthermore, we showed for the first time that *HNF1B* deletion, rather than intragenic mutation, is associated with a higher susceptibility to

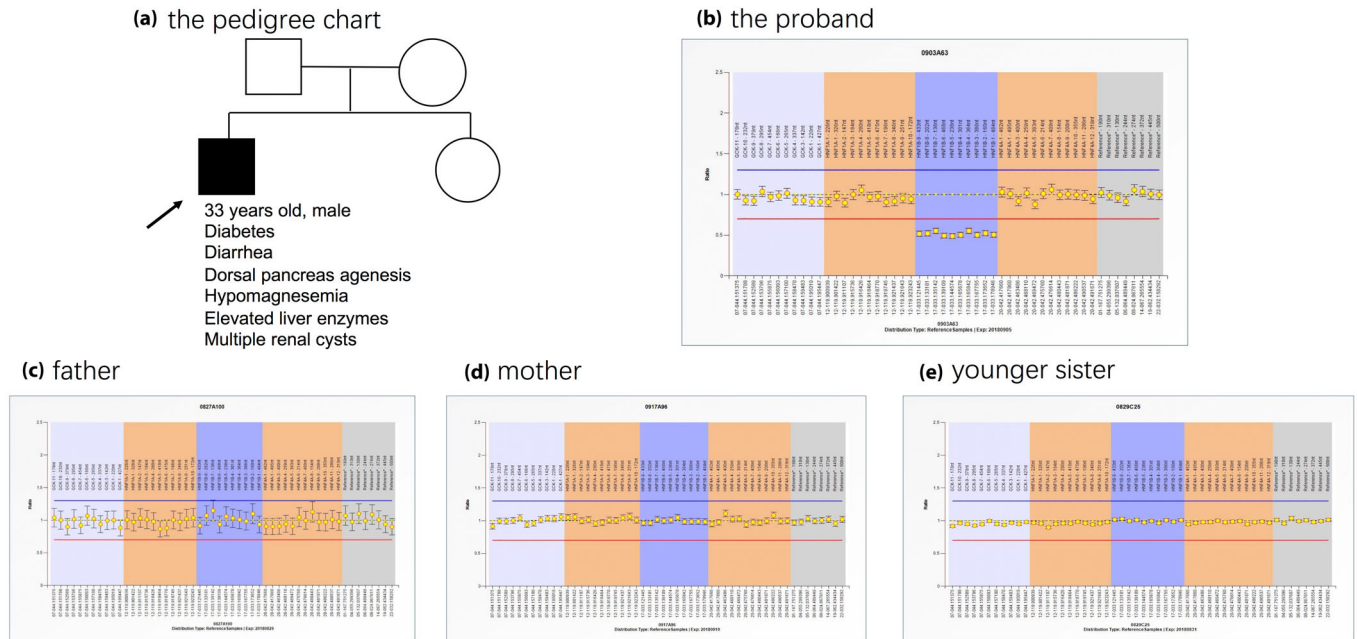


Figure 2 | Multiplex ligation-dependent probe amplification showed a de novo heterozygous whole hepatocyte nuclear factor 1B (*HNF1B*) deletion in the proband. (a) The pedigree chart of the family. (b–e) The multiplex ligation-dependent probe amplification results of the proband and family members. The multiplex ligation-dependent probe amplification kit contained probes detecting the maturity-onset diabetes of the young 5 gene, *GCK*, *HNF1A*, *HNF1B* and *HNF4A*. The fluorescence signal between 0.7 and 1.33 (from the red horizontal line to blue horizontal line) was considered to be normal. A heterozygous whole *HNF1B* deletion was found in the proband (the ellipse in b).

Table 3 | Genotype–phenotype correlation of hypomagnesemia in *HNF1B* syndrome

	Hypomagnesemia	Normomagnesemia	Total (n)	Frequency (%) [†]	OR (95% CI)	P-value
Deletion	84	52	136	61.8	3.1 (1.8, 5.4)	<0.001
Intragenic mutation	31	60	91	34.1		
Total (n)	115	112	227	50.7		

[†]Frequency of hypomagnesemia. CI, confidence interval; OR, odds ratio.

hypomagnesemia, supported by a large sample size. When diabetes is concomitant with multisystem phenotypes, *HNF1B* syndrome should be taken into consideration. The utilization of the *HNF1B* score is valuable for screening potential *HNF1B* candidates, and the understanding of the genotype–phenotype association provides significant assistance to endocrinologists in selecting appropriate methods for detecting *HNF1B* deletion or intragenic mutation, devising treatment plans and evaluating prognosis.

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JH). We appreciate the cooperation from Mr Pan, the patient reported in the study, and his family, and congratulate Mr Pan for getting married after discharge and having two healthy daughters.

DISCLOSURE

The authors declare no conflict of interest. Approval of the research protocol: This study was approved by the ethics committee of The Second Xiangya Hospital of Central South University (No. 2019-Research-40), and carried out according to the principles of the Declaration of Helsinki in 1995 (as revised in Fortaleza, Brazil, October 2013). Informed consent: The patient provided his written informed consent to participate in this study. Registry and the registration no. of the study/trial: N/A. Animal studies: N/A.

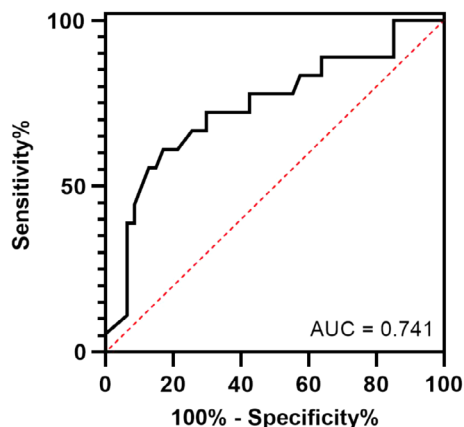


Figure 3 | The receiver operating characteristic curve showed that serum magnesium concentration had a high predictive value in diagnosing hepatocyte nuclear factor 1B deletion or intragenic mutation. AUC, area under the curve.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | The case number with both HNF1B genotype and serum magnesium status in each publication.

Table S2 | The number of cases with both HNF1B genotype (categorized as Deletion, Missense mutation, Nonsense mutation, Splice-site mutation) and serum magnesium status in each publication.

Table S3 | Genotypes (categorized as Deletion, Missense mutation, Nonsense mutation, Splice-site mutation)-Phenotypes of hypomagnesemia in HNF1B syndrome.