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ORIGINAL ARTICLE

Diagnostic strategy for inherited hypomagnesemia

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Abstract
Background Hereditary hypomagnesemia is difficult to diagnose accurately because of its rarity and the variety of causative genes. We established a flowchart for identifying responsible genes for hypomagnesemia, and we confirmed its diagnostic efficacy in patients with suspected inherited hypomagnesemia.
Methods We established a flowchart and applied it to five index cases with suspected inherited hypomagnesemia. Direct sequence analysis was used to detect the causative gene variants in four cases, and targeted sequencing analysis using next-generation sequencing (NGS) of all causative genes for hypomagnesemia was used in one.
Results Expected pathogenic variants were detected in the *HNF1B, TRPM6, CLDN16, CASR*, or *SLC12A3* gene in all five cases. The results of all genetic analyses were consistent with the clinical diagnostic results using the flowchart.
Conclusions Accurate genetic diagnosis is crucial for estimating the prognosis, detecting complications in organs other than the kidneys, and for directing genetic counseling. The developed flowchart for identifying responsible genes for hypomagnesemia was useful for diagnosing inherited hypomagnesemia. In addition, NGS analysis will help to resolve clinical difficulties in making an accurate diagnosis and thus improve the diagnostic strategy for inherited hypomagnesemia.

Keywords Hereditary hypomagnesemia · Diagnostic flowchart · Next-generation sequencing

Introduction

Magnesium (Mg^{2+}) is a cofactor for a group of enzymes and transporters, and it also plays an essential role in the synthesis of nucleic acids and proteins [1]. Hypomagnesemia is defined as a serum Mg^{2+} level < 1.7 mg/dL (<0.7 mmol/L) [2]. Patients with hypomagnesemia suffer from nonspecific symptoms such as depression, tiredness, muscle spasms, or muscle weakness [1], while severe Mg^{2+} depletion (<0.4 mmol/L) may lead to cardiac arrhythmias, tetany, or seizures [1]. Hypomagnesemia can be caused by many triggers, including alcohol abuse, chronic diabetes, drugs, or eclamptic seizures [3], while genetic hypomagnesemia can be distinguished from Mg^{2+} deficiency arising from other causes [1]. However, the genetic causes of hypomagnesemia are also heterogeneous and comprise both recessive and dominant disorders (Table 1) [2].

Hereditary hypomagnesemia may be difficult to diagnose, because it is a relatively rare disorder and exhibits a variety of clinical presentations. We established a flowchart for identifying responsible genes for hypomagnesemia (Fig. 1) and demonstrated its efficacy in five index cases.

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Table 1 Genetic causes of hypomagnesemia

	Gene	Protein	Inheritance
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	*CLDN16*	Claudin-16	AR
Familial Hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement	*CLDN19*	Claudin-19	AR
Autosomal dominant hypomagnesemia with hypocalciuria	*FXYD2*	γ-Subunit of the Na-K-ATPase	AD
Isolated recessive hypomagnesemia	*EGF*	pro-EGF	AR
Hypomagnesemia with secondary hypocalcemia	*TRPM6*	TRPM6	AR
Autosomal dominant hypomagnesemia	*KCNA1*	Voltage gated K channel Kv1.1	AD
Autosomal dominant hypomagnesemia	*CNNM2*	CNNM2	AD
Autosomal dominant hypomagnesemia with CAKUT	*HNF1B*	Hepatocyte nuclear factor 1 homeobox B	AD
Gitelman syndrome	*SLC12A3*	NCCT	AR
Type3 Bartter syndrome	*CLCNKB*	ClC-Kb	AR
Type4 Bartter syndrome	*BSND*	Barttin	AR
Autosomal dominant hypocalcemia	*CASR*	Ca sensing receptor	AD
Epilepsy, ataxia, sensorineural deafness, and tubulopathy syndrome	*KCNJ10*	Kir4.1	AR
Hyperphenylalaninemia and primapterinuria/renal cyst and diabetes-like	*PCBD1*	PCBD1	AR
neonatal inflammatory skin and bowel disease-2	*EGFR*	EGFR	AR
Kenny-Caffey syndrome type 2	*FAM111A*	FAM111A	AD

AR autosomal recessive, *AD* autosomal dominant, *CAKUT* congenital anomalies of the kidney and urinary tract

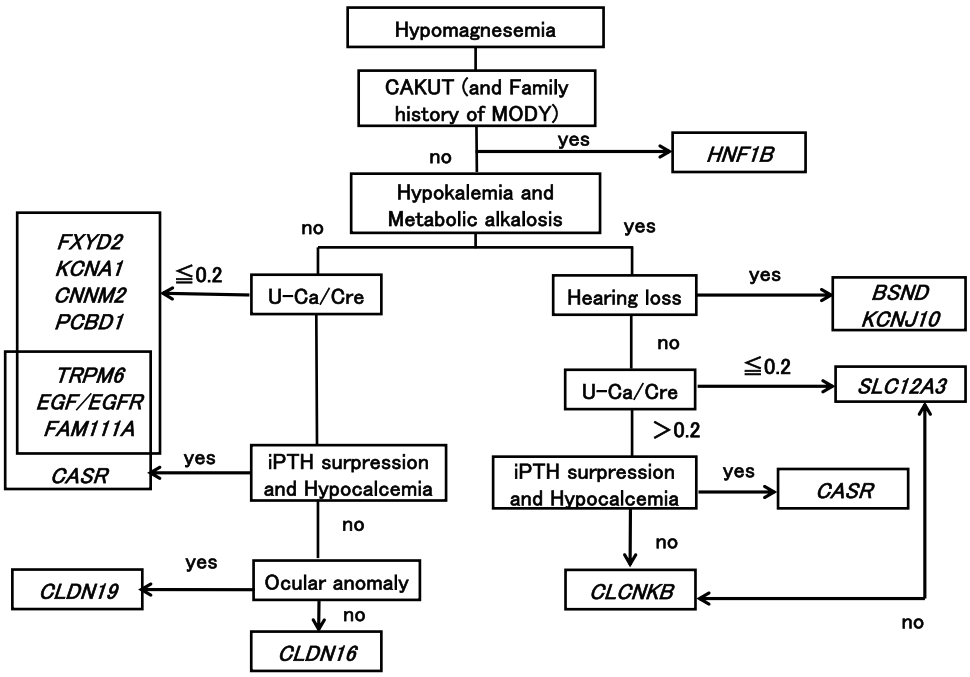

Fig. 1 Flowchart for identifying responsible genes for hypomagnesemia. The flowchart required the following clinical data for identifying responsible genes for hypomagnesemia: (*1*) congenital anomalies of the kidney and urinary tract (CAKUT) or family history of maturity-onset diabetes of the young (MODY); (*2*) hypokalemia and metabolic alkalosis (Gitelman-like); (*3*) hearing loss; (*4*) hypo or hypercalciuria; (*5*) hypoparathyroidism and hypocalcemia; and (*6*) ocular anomalies

Materials and methods

Patients

We investigated five index cases with hypomagnesemia (Table 2). Clinical and laboratory data and pathological findings were obtained from medical records.

Genetic analysis

Genomic DNA was isolated from peripheral blood leukocytes from the patients and their family members using the Quick Gene Mini 80 system (Wako Pure Chemical Industries, Ltd., Tokyo, Japan) according to the manufacturer's instructions. Direct sequencing or next-generation sequencing (NGS) was conducted for

Table 2 Clinical characteristics and results of genetic diagnoses of index cases

Parameter	Patient 1	Patient 2		Younger Brother	Patient 3	Elder sister	Patient 4	Patient 5
Sex and age	Male, 2 years old	Male, 1 month old	Current data (26 years old)	Current data (21 years old)	Female, 6 months old	Female, 4 years old	Female, 33 years old	Female, 8 years old
Clinical manifestation	CAKUT	–	–	–	–	–	–	–
Serum indices								
K^+, mEq/L	4.1	4.5	4.2	4	5.5	4.2	3	2.2
Ca^{2+}, mg/dL	10.2	2.9	9.2	8.9	6.3	9.3	6.2	10.1
Mg^{2+}, mg/dL	1.5	0.3	1	1.1	0.8	1.4	1.2	0.6
HCO_3^-, mmol/L					14.8	25.4	30.6	30.3
pH	7.354	7.425			7.369	7.385	7.568	7.459
Creatinine, mg/dL	0.47		0.85	0.69	0.3	0.41	1.54	0.26
Intact PTH, pg/mL	N/A	45.5	19	35	71	–	Below detectable levels	73
Urinary indices								
FEMg, %	N/A		0.38	0.23	19	–	11.26	5.7
Ca^{2+}/creatinine, g/g cre	Below detectable levels		0.02	0.007	2.1	0.15	0.33	0.01
β2MG, μg/L	155		168	<60	301	Below detectable levels	1220	5.7
Echogram	Renal cysts and bilateral renal hypoplasia	Normal	Normal	Normal	Bilateral renal calcification	Bilateral renal calcification	Bilateral renal calcification	Normal
Genes	*HNF1B*	*TRPM6*			*CLDN16*		*CASR*	*SLC12A3*
Nucleotide change	c.1007insC	c.5084-2A > G (Homo)			c.414delT c.715G > T		c.2363T > G	c.1844C > T (Homo)
Consequence on protein level	p.(His336HfsX23)	Exon 31 skip?			p.(Ala139ArgfsX5) p.(Gly239*)		p.(Phe788Cys)	p.(Ser615Leu)

CAKUT congenital anomalies of the kidney and urinary tract, *N/A* not analyzed

genes responsible for inherited hypomagnesemia. NGS samples were prepared using a HaloPlex target enrichment system kit (Agilent Technologies, Santa Clara, CA) according to the manufacturer's instructions. The inherited hypomagnesemia-responsible genes *CLCNKB, BSND, SLC12A3, CASR, KCNJ10, CLDN16, CLDN19, FXYD2, EGF, TRPM6, KCNA1, CNNM2*, and *HNF1B* were screened by targeted sequencing.

Ethical considerations

All procedures were approved by the Institutional Review Board (IRB) of Kobe University Graduate School of Medicine and in accordance with the Helsinki Declaration of 1975, as revised in 2000 (IRB number: 301). Informed consent was obtained from all index patients or their parents.

Results

Patients

Patient 1 was a 2-year-old boy who was found to have low serum Mg^{2+} by chance at a regular visit for observation of hypoplastic kidney. He had been born at 36 weeks to unrelated parents after a hydramniotic pregnancy, with a birth weight of 2250 g. His father has an isolated renal cyst and diabetes mellitus, his older sister had died immediately after birth because of Potter's sequence, and his younger brother also had renal hypoplasia. Laboratory test results are shown in Table 2. According to the flowchart, *HNF1B* gene mutation was suspected based on the clinical presentation in this family with CAKUT and diabetes, and direct sequencing of this gene was conducted.

Patient 2 was a 26-year-old man. He had been born at 39 weeks to unrelated parents after an uncomplicated pregnancy, with a birth weight of 2700 g. He presented with recurrent seizures at 1 month old, and although laboratory tests revealed hypomagnesemia and hypocalcemia, no further examination was conducted at that time. His younger brother underwent blood tests at 4 days old because of his family history, which also revealed hypomagnesemia. The results of laboratory tests for the index patient performed at 1 month old are shown in Table 2. He required intravenous Mg^{2+} two or three times a week since the initial diagnosis. This patient had no ocular involvement. His and his brother's current laboratory data are shown in Table 2. We conducted targeted sequencing analysis using NGS, including hereditary hypomagnesemia-causative genes. Based on the clinical presentation of hypomagnesemia and hypocalcemia and intact parathyroid hormone (iPTH) suppression without CAKUT, hypokalemia, or hypercalciuria, this family was suspected to have *TRPM6, EGF/EGFR, or FAM111A* variants.

Patient 3 was a 6-month-old girl who was born to unrelated parent at 38 weeks after an uncomplicated pregnancy, with a birth weight of 2680 g. Low serum Ca^{2+} and Mg^{2+} were detected by chance during a bout of viral gastroenteritis. Her asymptomatic elder sister was tested after the diagnosis of Patient 3 and was also found to have hypomagnesemia. Laboratory test results for both sisters are shown in Table 2. She had no ocular involvement. The clinical presentation of hypercalciuria without CAKUT, hypokalemia, iPTH suppression, or ocular abnormality suggested *CLDN16* mutation, and direct sequencing of this gene was conducted.

Patient 4 was a 33-year-old woman, whose case has been reported previously [4]. Low serum Ca^{2+} was detected by chance in the absence of any clinical signs, and she was diagnosed with hypocalcemia and hypoparathyroidism at the age of 6 years. She showed hypokalemia, metabolic alkalosis, and short stature at the age of 12, and was administered growth hormone therapy for 3 years. Hypomagnesemia was detected when she was 25 years old. She developed bilateral renal calcification and mild impairment of kidney function at the age of 33 years. She had been prescribed active vitamin D3 since the age of 6 years, but this was tapered off after a diagnosis of ADH1. The results of laboratory tests performed at her initial visit to our hospital are shown in Table 2. From the clinical presentation of hypokalemia, hypercalciuria, iPTH suppression, and hypocalcemia without CAKUT or hearing loss, she was suspected to be have a *CASR* mutation, and direct sequencing of this gene was conducted.

Patient 5 was an 8-year-old girl who had been born at 40 weeks to unrelated parents after an uncomplicated pregnancy, with a birth weight of 3246 g. She had no remarkable family or past history. However, low serum Mg^{2+} was detected by chance when she was affected by viral gastroenteritis. Her laboratory test results are shown in Table 2. She had no significant inner ear involvement. Based on her clinical presentation of hypokalemia and hypocalciuria, without hearing loss, she was suspected to have an *SLC12A3* mutation.

Flowchart

The flowchart was established according to the following reports of inherited hypomagnesemia. *HNF1B* is a causative gene of CAKUT and early onset diabetes, and *MODY5* that is also caused by *HNF1B* variants is frequently accompanied by hypomagnesemia [5–7]. Patients with *FXYD2, KCNA1, CNNM2*, or *PCBD1* variants show hereditary hypomagnesemia with hypo- to normocalciuria [8–12]. Hypomagnesemia with secondary hypocalcemia (HSH) caused by *TRPM6* variants is associated with hypo- to normocalciuria with serum iPTH suppression [13–15]. Kenny-Caffey syndrome type 2 is a rare condition caused by *FAM111A* variants. It is characterized by cortical thickening and medullary stenosis of tubular bones, delayed closure of the anterior fontanelle, eye abnormalities, hypoparathyroidism and hypocalcemia accompanied by hypomagnesemia, and hypo- to normocalciuria [16]. ADH1/type V Bartter syndrome caused by *CASR* variants also shows iPTH supression and hypocalcemia [17–19]. Patients with *EGF* or *EGFR* variants may share similar pathophysiology with HSH, because EGF increases TRPM6 activity and surface expression [20, 21]. Familial hypomagnesemia with hypocalcemia and nephrocalcinosis (FHHNC) caused by *CLDN16* or *CLDN19* variants is associated with hypercalciuria, while *CLDN19* variants are associated with ocular impairment [22–24]. Hypomagnesemia accompanied by hypokalemia and metabolic alkalosis (Gitelman-like) indicates the possibility of Bartter/

Gitelman syndrome-associated disorders. Both type III Bartter syndrome caused by variants in *CLCNKB* and Gitelman syndrome caused by variants in *SLC12A3* are usually accompanied by hypomagnesemia [25–28]. Pathogenic variants in the *BSND* gene cause type IV Bartter syndrome with sensorineural deafness and occasionally hypomagnesemia [2, 29]. Pathogenic variants in *KCNJ10* also cause hypokalemic and hypomagnesemic tubulopathy with hearing loss (EAST syndrome), and this tubulopathy is identical to that seen in Gitelman syndrome [30].

The flowchart required the following clinical data for identifying responsible genes for hypomagnesemia: (1) congenital anomalies of the kidney and urinary tract (CAKUT) or family history of maturity-onset diabetes of the young (MODY); (2) hypokalemia and metabolic alkalosis (Gitelman-like); (3) hearing loss; (4) hypo- or hypercalciuria; (5) hypoparathyroidism and hypocalcemia; and (6) ocular anomalies (Fig. 1).

Genetic analysis

All genetic test results are shown in Tables 2 and 3. The results of all genetic analyses were consistent with the clinical diagnostic results obtained using the flowchart (Fig. 1). Truncating variants were detected in Patients 1 and 3. A splicing variant was detected in Patient 2. Missense variants were detected in Patients 4 and 5, both of which were predicted as pathogenic by in silico analysis. In addition, variants in Patients 1, 2, 4 and 5 have been reported as pathogenic (Table 3) [31–34].

Discussion

This study demonstrated the validity of our flowchart in five index cases of inherited hypomagnesemia. The flowchart is necessarily complicated because of the genetic heterogeneity of the condition. However, an accurate clinical diagnosis is important in terms of the kidney prognosis, the presence of complications other than hypomagnesemia, and for conducting genetic counseling. Recent developments in genetic techniques mean that it is possible to make a genetic diagnosis using NGS, even in the absence of an accurate clinical diagnosis, as in Patient 2. However, a clinical diagnosis remains important, because NGS is not always available. A diagnostic flowchart thus provides a highly useful tool for clinicians.

Heterozygous variants in *HNF1B* result in multi-system disorders and are the most common monogenic cause of CAKUT, occurring in 10–30% of CAKUT patients in the prenatal period [7]. *HNF1B* is also a causative gene of early onset diabetes, MODY5 [6]. In addition, an initial report showed that hypomagnesemia occurred in up to 50% of affected patients [5]. The presence of CAKUT with hypomagnesemia and a family history of diabetes provided a useful clue to a potential *HNF1B* mutation in Patient 1. Serum Mg^{2+} levels should be monitored in patients with CAKUT as an indicator of potential *HNF1B* mutations, while a family history of early onset diabetes is also a clue for the detection of *HNF1B* variants, as in Patient 1.

Homozygous or compound heterozygous variants in *TRPM6* cause HSH, which is a relatively rare autosomal recessive disease [15]. Affected individuals present in early

Table 3 Results of genetic diagnosis

Patient	Genes	Inheritance mode	Nucleotide changes	Consequence on protein level	Previous reports	Variant types	SIFT	PolyPhen2
1	*HNF1B*	AD	c.1006dupC	p.(His336HfsX23)	Mache (2002) Pediatric Nephrol 17, 1021	Frameshift	–	–
2	*TRPM6*	AR	c.5084-2A > G (Homo)	(Exon 31 skip?)	Lainez (2014) Eur J Hum Genet 22, 497	Splice site variant	–	–
3	*CLDN16*	AR	c.414delT	p.(Ala139ArgfsX5)	Novel	Frameshift	–	–
			c.715G > T	p.(Gly239*)	Novel	Nonsense variant	–	–
4	*CASR*	AD	c.2363T > G	p.(Phe788Cys)	Watanabe (1998) J Clin Endocrinol Metab 83, 2497	Missense variant	Damaging (0.01)	Probably damaging (1.00)
5	*SLC12A3*	AR	c.1844C > T (Homo)	p.(Ser615Leu)	Cruz (2001) Kidney Int 59, 710	Missense variant	Damaging (0.01)	Probably damaging (1.00)

infancy with seizures caused by the severe hypocalcemia and hypomagnesemia [15]. HSH is sometimes misdiagnosed as primary hypoparathyroidism because of its initial presenting symptoms of hypocalcemia and concomitant low or inappropriate normal parathyroid hormone (PTH) caused by hypomagnesemia, which blocks the release of PTH and decreases sensitivity to circulating PTH in target organs [13]. Some HSH patients can be managed by Mg^{2+} supplementation without a genetic diagnosis, as in Patient 2. HSH is a relatively rare condition, and the causative mutation in Patient 2 was detected by NGS analysis; however, our flowchart also led to a diagnosis of HSH in this patient.

Loss-of-function mutations in the genes for claudin-16 and its close relative claudin-19 lead to an identical renal phenotype, with combined renal Ca^{2+} and Mg^{2+} wasting and nephrocalcinosis, referred to as FHHNC, inherited in an autosomal dominant mode [23, 24]. FHHNC is frequently complicated by progressive renal failure and the renal prognosis is poor, with progressive chronic kidney disease requiring renal replacement therapy typically occurring in the second or third decades of life [35]. Patients with *CLDN16* and *CLDN19* variants may have different renal prognoses; *CLDN19* mutations are associated with a higher risk of chronic kidney disease and end-stage renal disease, and ocular impairment occurs exclusively in patients with *CLDN19* mutations [22]. Definitive genetic diagnosis may be useful to prediction of prognosis or phenotype in FHHNC patients.

Gain-of-function mutations in *CASR* cause ADH1, which is associated with hypocalcemia, relative hypercalciuria, and inadequate PTH secretion, and occasionally with hypomagnesemia [17]. In some cases, ADH1 is accompanied by hypokalemia, and this combination may be classified as type V Batter syndrome [18, 19]. In addition to HSH, ADH1 may also be misdiagnosed as primary hypoparathyroidism, as in Patient 4.

Loss-of-function mutations in *SLC12A3* cause Gitelman syndrome, which is an autosomal recessive renal tubulopathy characterized by hypokalemic metabolic alkalosis with hypocalciuria and hypomagnesemia [28]. Type III Batter syndrome, which is caused by *CLCNKB* variants, frequently shows phenotypic overlap with Gitelman syndrome [25–27], and some type III Batter syndrome patients may show clinical features of Gitelman syndrome, such as hypomagnesemia and hypocalciuria [25, 26]. It is not possible to make a definite diagnosis in such cases without genetic testing; however, a definitive genetic diagnosis will allow better management of patients and appropriate pathophysiological investigation of the disease.

Our flowchart was useful in the five index cases of inherited hypomagnesemia, and was also validated in the previous cases of inherited hypomagnesemia. However, many genes are involved in inherited hypomagnesemia, some of which have been reported in too few cases to define their characteristics. For instance, hypomagnesemia associated with variants in *KCNA1* [9] or loss-of-function in the *EGFR* gene [20] has only been reported in one pedigree and one patient, respectively, though there have been some reports of cases with hypomagnesemia treated with cetuximab, a monoclonal antibody directed against EGFR [36]. Phenotypic overlap, such as that between Gitelman syndrome and type III Bartter syndrome [25, 26], or diversity of clinical phenotypes associated with gain-of-function mutations in *CASR* causing ADH1 and type V Bartter syndrome, will complicate the flowchart [18, 19, 37]. Further studies of inherited hypomagnesemia are, therefore, required to improve the flowchart.

In conclusion, hereditary hypomagnesemia may be difficult to diagnose accurately because of its rarity and the variety of causative genes. Our flowchart for identifying responsible genes for hypomagnesemia provides a useful diagnostic tool, but some kinds of hereditary hypomagnesemia still require genetic testing to reach a definite diagnosis. NGS analysis will help to resolve clinical difficulties and improve the chance of making a definite diagnosis in patients with hereditary hypomagnesemia.

Compliance with ethical standards

All procedures were approved by the Institutional Review Board (IRB) of Kobe University Graduate School of Medicine and in accordance with the Helsinki Declaration of 1975, as revised in 2000 (IRB number: 301). Informed consent was obtained from all index patients or their parents.

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Conflict of interest The authors have nothing to disclose.

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