

Hereditary kidney diseases associated with hypomagnesemia

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In the kidney, a set of proteins expressed in the epithelial cells of the thick ascending loop of Henle and the distal convoluted tubule directly or indirectly play important roles in the regulation of serum magnesium levels. Magnesium reabsorption in the thick ascending loop of Henle occurs through a passive paracellular pathway, while in the distal convoluted tubule, the final magnesium concentration is established through an active transcellular pathway. The players involved in magnesium reabsorption include proteins with diverse functions including tight junction proteins, cation and anion channels, sodium chloride cotransporter, calcium-sensing receptor, epidermal growth factor, cyclin M2, sodium potassium adenosine triphosphatase subunits, transcription factors, a serine protease, and proteins involved in mitochondrial function. Mutations in the genes that encode these proteins impair their function and cause different rare diseases associated with hypomagnesemia, which may lead to muscle cramps, fatigue, epileptic seizures, intellectual disability, cardiac arrhythmias, and chronic kidney disease. The purpose of this review is to describe the clinical and genetic characteristics of these hereditary kidney diseases and the current research findings on the pathophysiological basis of these diseases.

Keywords: Hypomagnesemia, Magnesium handling, Mutation, Rare diseases, Renal tubulopathies

Introduction

Magnesium (Mg^{2+}), the second-most abundant intracellular cation, is an indispensable ion for many cellular functions including energy metabolism and nucleic acid and protein synthesis [1]. Mg^{2+} is also a regulator of sodium, potassium, and calcium channels. Therefore, serum Mg^{2+} levels, which are usually 0.70 to 1.1 mmol/L, need to be precisely controlled. Hypomagnesemia is defined as serum Mg^{2+} level below 0.7 mmol/L. The predominant laboratory tests used for the diag-

nosis of hypomagnesemia are the serum Mg^{2+} concentration and the 24-hour urinary Mg^{2+} tests. In cases in which the serum Mg^{2+} level is low, a 24-hour urine Mg^{2+} higher than 24 mg/day suggests renal Mg^{2+} wasting as the cause of the hypomagnesemia, while values lower than 24 mg/day indicate deficient Mg^{2+} intake and/or gastrointestinal losses. Magnesium homeostasis is determined by intestinal absorption, renal reabsorption, and storage in bone. In the kidney and intestine, these processes involve a combination of paracellular and transcellular epithelial transport routes.

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Hypomagnesemia may cause muscle cramps, fatigue, appetite loss, and disruptions in calcium and potassium homeostasis [1]. Acute hypomagnesemia may lead to more serious consequences like epileptic seizures, intellectual disability, and cardiac arrhythmias. Causes of hypomagnesemia include type 2 diabetes, gastrointestinal diseases, alcoholism, use of diuretics or other medications, dietary deficiency, and genetic defects. Over the last two decades, clinical and genetic studies of patients with rare hereditary disorders of Mg^{2+} handling have enabled the identification of important components of epithelial Mg^{2+} transport in the kidney [2].

After passing the glomerular filter, 90% to 95% of the filtered Mg^{2+} is subsequently reabsorbed along the nephron [1]. Approximately 10% to 25% of the Mg^{2+} is reabsorbed by the proximal tubule (PT), 50% to 70% is reabsorbed by the thick ascending limb of the loop of Henle (TAL), and 5% to 10% is reabsorbed by the distal convoluted tubule (DCT) (Fig. 1). In the PT, Mg^{2+} reabsorption occurs in a passive paracellular mode. The mechanisms that control this process are unknown. In the TAL, Mg^{2+} reabsorption also takes place through a passive paracellular pathway, which is facil-

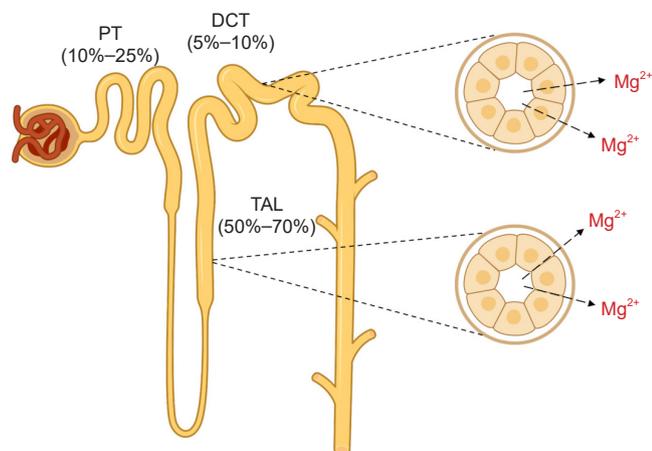


Figure 1. Schematic drawing of Mg^{2+} reabsorption by different segments of the nephron. Mg^{2+} is filtered at the glomerulus. In the proximal tubule (PT), about 10% to 25% of the initially filtered load of Mg^{2+} is reabsorbed through a passive paracellular route that remains poorly understood. The thick ascending limb of the loop of Henle (TAL) reabsorbs approximately 50% to 70% of the filtered load of Mg^{2+} by a passive paracellular transport. The remaining 5% to 10% of the filtered Mg^{2+} is reabsorbed in the distal convoluted tubule (DCT) through an active transcellular route. Approximately 95% of filtered Mg^{2+} is reabsorbed along the nephron.

itated by tight junction proteins claudin-16 and claudin-19 (Fig. 2) [3,4]. The basolateral calcium-sensing receptor (CaSR) controls the paracellular transport of calcium (Ca^{2+}) and Mg^{2+} by regulating the claudin-16/claudin-19 channel function through a signaling pathway [5]. In contrast, the main K^+ secretory channel in the kidney, the renal outer medullary K^+ channel (ROMK), which is located in the apical membrane of the TAL, plays a key role in the generation of the lumen-positive potential in TAL [1]. The renal chloride (Cl^-) channel CIC-Kb, which is located in the basolateral membrane of the TAL and also the DCT, facilitates the efflux of Cl^- to the interstitium [6]. The DCT establishes the final Mg^{2+} concentration through active transcellular

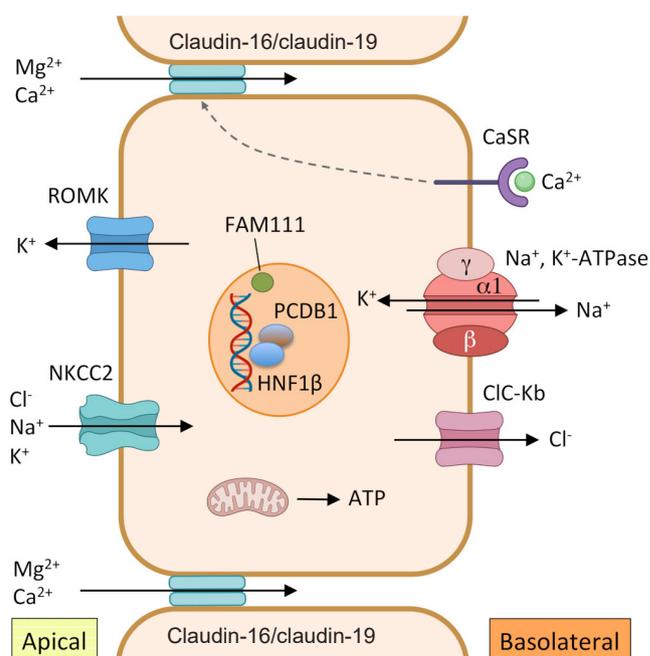


Figure 2. Reabsorption of Mg^{2+} in the TAL. In this segment of the nephron, Mg^{2+} reabsorption takes place through a passive paracellular pathway via claudin-16/claudin-19 channels located in the tight junctions. This transport depends on the driving force generated by the joint actions of Na^+ , K^+ -adenosine triphosphatase (ATPase), and Cl^- channel CIC-Kb, both located in the basolateral membrane, and Na^+ , K^+ -2Cl⁻-cotransporter (NKCC2) and renal outer medullary K^+ channel (ROMK), the main K^+ secretory channel in the kidney, located in the apical membrane. Basolateral calcium-sensing receptor (CaSR) indirectly regulates the paracellular divalent cation transport and the transcellular NaCl transport in the TAL.

ATP, adenosine triphosphate; HNF1 β , hepatocyte nuclear factor-1 beta; PCBD1, pterin-4 α -carbinolamine dehydratase; TAL, thick ascending limb of the loop of Henle.

reabsorption, which is highly regulated, via transient receptor potential melastatin type 6 (TRPM6) Mg^{2+} channels located in the apical membrane [7] (Fig. 3). TRPM6 needs to form heterotetramers with its close homolog TRPM7 to function [8]. The protein(s) that facilitates Mg^{2+} efflux from the basolateral side to the blood compartment has not been identified [9]. Cyclin M2 (CNNM2) and solute carrier family member A1 (SLC41A1) have been proposed as likely candidates for this function, but this subject is still under debate [10–12]. Other proteins involved, albeit indirectly, in Mg^{2+}

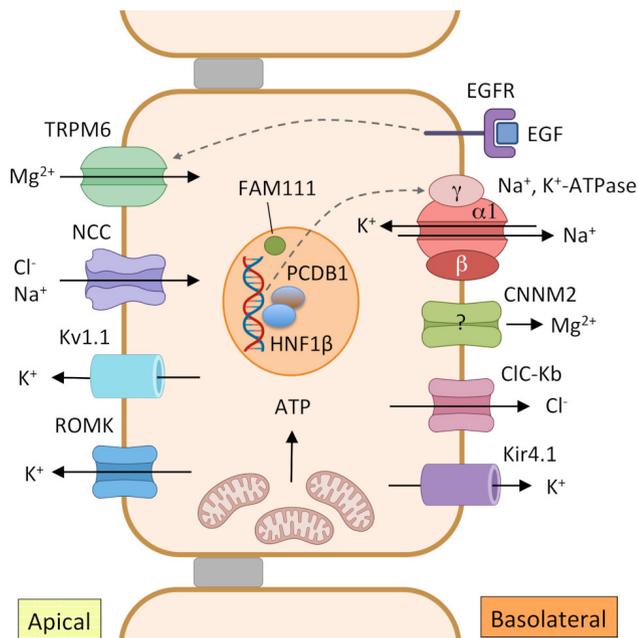


Figure 3. Reabsorption of Mg^{2+} in the DCT. In this tubular segment, Mg^{2+} is reabsorbed through a transcellular pathway. The apical Mg^{2+} channel transient receptor potential melastatin type 6 (TRPM6) facilitates transport of Mg^{2+} from the lumen to the epithelial cell. The driving force needed for Mg^{2+} transport is generated by the joint actions of Na^+ , K^+ -adenosine triphosphatase (ATPase), the Cl^- channel CIC-Kb and the K^+ channel Kir4.1 in the basolateral membrane and Na^+ - Cl^- cotransporter (NCC) and K^+ secretory channels Kv1.1 and renal outer medullary K^+ channel (ROMK) in the apical membrane. Epidermal growth factor (EGF) is implicated in the regulation of Mg^{2+} reabsorption through TRPM6. HNF1 β with coactivator pterin-4 α -carbinolamine dehydratase (PCDB1) increase transcription of the γ subunit of the Na^+ , K^+ -ATPase. Cyclin M2 (CNNM2) is a candidate for basolateral extrusion of Mg^{2+} or a regulator of Mg^{2+} transport, but this has not been experimentally confirmed.

ATP, adenosine triphosphate; DCT, distal convoluted tubule; EGFR, epidermal growth factor receptor; HNF1 β , hepatocyte nuclear factor-1 beta.

transport in the DCT include epidermal growth factor (EGF), a hormone that regulates the expression of TRPM6 on the apical membrane, basolateral Na^+ , K^+ -adenosine triphosphatase (ATPase), and K^+ channel Kir4.1, and the apical K^+ channel Kv1.1 and Na^+ Cl^- cotransporter (NCC) [13–16]. The last four proteins participate in the generation of the driving force needed for Mg^{2+} transport [9]. Mutations in any of the above proteins, except SLC41A1, which are involved directly or indirectly in Mg^{2+} transport, have been shown to cause hypomagnesemia (Table 1).

In this review, we present the current knowledge of hereditary kidney diseases associated with hypomagnesemia. We discuss the clinical characteristics and genetic information for each disease and describe the pathophysiological basis that has been proposed for some of the diseases, although in general these remain incompletely understood. We classified hypomagnesemias in three groups according to the implicated genes (Table 1). Group 1 includes hypomagnesemias associated with genes that encode proteins directly involved in Mg^{2+} transport and the regulatory proteins. Group 2 contains hypomagnesemias associated with genes encoding proteins involved in transport of other ions or their regulators, which indirectly affect Mg^{2+} handling. Group 3 includes hypomagnesemias associated with genes required for mitochondrial function, which also indirectly result in Mg^{2+} loss.

Group 1 hypomagnesemias

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis types 1 and 2

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive tubular disorder characterized by excessive urinary loss of Mg^{2+} and Ca^{2+} , bilateral nephrocalcinosis, and progressive chronic kidney disease (CKD) [17]. FHHNC patients typically present during early childhood or before adolescence with recurrent urinary tract infections, polyuria, polydipsia, nephrolithiasis, and failure to thrive [18–21]. FHHNC patients may show a pronounced decline in glomerular filtration rate at the time of diagnosis, and approximately one-third of cases progress to chronic renal failure during childhood or adolescence [21,22]. In contrast to patients with other hypomagnesemias, FHHNC patients have high serum levels of

Table 1. Inherited diseases associated with hypomagnesemia

Disorder	Associated gene	Protein ^a	Inheritance	OMIM #
Group 1				
FHHNC type 1	<i>CLDN16</i>	Claudin-16	AR	248250
FHHNC type 2	<i>CLDN19</i>	Claudin-19	AR	248190
Hypomagnesemia with secondary hypocalcemia	<i>TRPM6</i>	Mg ²⁺ channel TRPM6	AR	602014
Isolated recessive hypomagnesemia	<i>EGF</i>	Epidermal growth factor	AR	611718
NISBD2	<i>EGFR</i>	Epidermal growth factor receptor	AR	616069
HSMR type 1	<i>CNNM2</i>	Cyclin M2	AD/AR	616418/613882
Group 2				
Bartter syndrome type 3	<i>CLCNKB</i>	Cl ⁻ channel ClC-Kb	AR	607364
Gitelman syndrome	<i>SLC12A3</i>	Na ⁺ Cl ⁻ cotransporter	AR	263800
Autosomal dominant hypocalcemia with hypercalciuria	<i>CASR</i>	Calcium-sensing receptor CaSR	AD	601198
Episodic ataxia type 1	<i>KCNA1</i>	Voltage-gated K ⁺ channel Kv1.1	AD	160120
Isolated dominant hypomagnesemia	<i>FXYD2</i>	γ subunit of Na ⁺ , K ⁺ -ATPase	AD	154020
HSMR type 2	<i>ATP1A1</i>	α1 subunit of Na ⁺ , K ⁺ -ATPase	AD	618314
EAST/SeSAME syndrome	<i>KCNJ10</i>	K ⁺ channel Kir4.1	AR	612780
ADTKD- <i>HNF1B</i>	<i>HNF1B</i>	Transcription factor HNF1β	AD	137920
TNHP	<i>PCBD1</i>	PCBD1, dimerization cofactor of HNF1β	AR	264070
Kenny-Caffey syndrome type 2	<i>FAM111A</i>	Nuclear serine protease FAM111A	AD	127000
Group 3				
HHH syndrome	<i>MT-TI</i>	Isoleucine tRNA	Mitochondrial	500005
Kearns-Sayre syndrome	Large deletions	-	Mitochondrial	530000
HUPRA syndrome	<i>SARS2</i>	seryl-tRNA synthetase	AR	613845

AD, autosomal dominant; ADTKD-*HNF1B*, autosomal dominant tubulointerstitial kidney disease subtype *HNF1B*; AR, autosomal recessive; EAST/SeSAME, epilepsy, ataxia, sensorineural deafness and tubulopathy syndrome/seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance; FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; HHH, hypertension, hypercholesterolemia and hypomagnesemia; HSMR, hypomagnesemia, seizures, and mental retardation disorder; HUPRA, hyperuricemia, pulmonary hypertension, renal failure and alkalosis; NISBD2, neonatal inflammatory skin and bowel disease type 2; TNHP, transient neonatal hyperphenylalaninemia and primapterinuria; tRNA, transfer RNA.

^aAll the genes associated with hereditary hypomagnesemias encode proteins, except MT-TI, which encodes a tRNA.

parathyroid hormone (PTH) before the onset of chronic renal failure [1,19,23]. In some cases, patients present amelogenesis imperfecta [24,25]. Clinical signs of severe hypomagnesemia such as seizures and muscular tetany are rare.

FHHNC is caused by recessive mutations in *CLDN16* (FHHNC type 1, OMIM #248250) or *CLDN19* (FHHNC type 2, OMIM #248190) [3,4]. Patients with mutations in *CLDN19* also present ocular abnormalities such as severe myopia, nystagmus, and macular colobamata [4,21,26]. *CLDN16* and *CLDN19* encode the tight junction proteins claudin-16 and claudin-19, respectively, which are strongly expressed in the kidney [3,4]. Claudin-19 is also expressed in peripheral neurons and retina [4,27]. Claudin-16 and claudin-19 form heteromeric paracellular cation channels in the TAL that regulate Ca²⁺ and Mg²⁺ transport [28,29]. The reabsorption of Mg²⁺ is greatly dependent on the transepithelial poten-

tial as a driving force, which is created by a transepithelial NaCl concentration gradient. *CLDN16* and *CLDN19* mutations have been shown to impair the permeating function of these channels, resulting in a reduced lumen-positive potential and the simultaneous loss of the driving force for Mg²⁺ reabsorption [22,28].

Hypomagnesemia with secondary hypocalcemia

Hypomagnesemia with secondary hypocalcemia (HSH, OMIM #602014) is a rare autosomal recessive disorder characterized by severe hypomagnesemia associated with hypocalcemia. The levels of serum Mg²⁺ in patients with HSH are usually much lower than in patients with other types of hereditary hypomagnesemias [30]. The disease usually presents in early infancy, with neurological symptoms in-

cluding tetany and severe seizures that are refractory to anticonvulsant therapy [30,31]. HSH patients have very low serum levels of PTH. Persistent low levels of serum Mg^{2+} likely cause secondary hypocalcemia by inhibiting PTH secretion and inducing resistance at the receptor sites [30]. The main defect in HSH is a reduction in intestinal Mg^{2+} absorption, which is in contrast to all other identified hereditary hypomagnesemias, along with reduced Mg^{2+} reabsorption in the DCT with renal Mg^{2+} wasting [31,32].

HSH is caused by recessive loss-of-function mutations in the *TRPM6* gene, which encodes the TRPM6 cation channel [31,32]. TRPM6 is predominantly expressed in the apical membrane of the intestinal and renal DCT epithelial cells, where it is involved in Mg^{2+} reabsorption [7]. Its channel activity and expression are regulated by several factors including EGF and adenosine triphosphate (ATP) [14]. TRPM6 mutations identified in HSH patients disrupt Mg^{2+} conductance through the channel, both in the colon and DCT, causing hypomagnesemia [7]. However, the mechanisms leading to this disease are not entirely known. TRPM6 interacts with its close homolog TRPM7 to form functional heteromeric TRPM6/TRPM7 Mg^{2+} channels [8]. TRPM6 and TRPM7 contain a transmembrane ion channel segment covalently joined to a cytosolic serine/ threonine protein kinase domain at the carboxy terminus. The kinase domain is cleaved from the channel segment and, after its translocation to the nucleus, it regulates the transcription of many genes involved in development [33]. Therefore, it has been suggested that TRPM6 may play a much wider role in the cell than only in Mg^{2+} homeostasis [33].

Isolated recessive hypomagnesemia

Isolated recessive renal hypomagnesemia is a rare disorder characterized by hypomagnesemia and normocalciuria [34]. Hypomagnesemia is due to renal Mg^{2+} wasting. Patients show seizures and neurodevelopmental delay during childhood. Only two affected girls from a consanguineous family have been reported, and no other biochemical abnormalities were identified in these patients. A homozygous missense mutation in the *EGF* gene coding for pro-EGF was identified as the underlying genetic defect [34]. Pro-EGF is a type I membrane-bound precursor protein that is proteolytically cleaved to generate the soluble EGF peptide hormone. EGF binds with high affinity to the renal epidermal growth

factor receptor (EGFR) at the basolateral membrane of the DCT. EGFR activation triggers a signaling cascade leading to an increase of TRPM6 channels on the apical membrane and increased Mg^{2+} reabsorption [14]. The disease-causing *EGF* mutation results in diminished sorting of pro-EGF, preventing adequate secretion of the EGF hormone [34]. This leads to inadequate stimulation of the EGFR, and therefore insufficient activation of the TRPM6 channel, which results in reduced reabsorption of Mg^{2+} .

Neonatal inflammatory skin and bowel disease type 2

Using whole-exome sequencing, a rare homozygous missense mutation (p.Gly428Asp) in *EGFR* was identified in a child with an inflammatory syndrome affecting the skin, bowel, and lungs (OMIM #616069) [35]. The pregnancy was complicated by polyhydramnios and the child was born prematurely. Laboratory tests revealed low serum levels of magnesium. The child showed failure to thrive and died at 2.5 years of age from widespread cutaneous and pulmonary infections in addition to electrolyte imbalance. Results of a skin biopsy and immunofluorescence microscopy studies revealed that the mutation p.Gly428Asp reduces EGFR plasma membrane localization [35].

Hypomagnesemia, seizures, and mental retardation disorder type 1

Hypomagnesemia, seizures, and mental retardation disorder (HSMR) type 1 is a complex rare condition characterized by renal Mg^{2+} loss that results in hypomagnesemia, infantile or juvenile epileptic seizures, and intellectual disability [36,37]. Patients also show autistic features, aggressive behavior, variable degrees of delayed psychomotor development, speech limitations, impaired motor skills, and in some cases obesity [37,38]. HSMR type 1 is caused by loss-of-function mutations in the *CNNM2* gene, which encodes the transmembrane protein CNNM2 [36–38]. Most HSMR type 1 patients carry heterozygous mutations that are generated *de novo* or inherited in an autosomal dominant pattern (OMIM #616418) [36–38]. However, a recessive mode of inheritance has been reported for several families [37,39]. Patients with recessive *CNNM2* mutations show a severe phenotype, including brain malformations, refractory epilepsy, and acute intellectual disability (OMIM

#613882).

CNNM2 is expressed in many organs and tissues including brain and kidney. In the kidney, *CNNM2* is predominantly expressed at the basolateral membrane of the DCT cells, where it is associated with Mg^{2+} reabsorption [36,40]. Whether *CNNM2* is itself an Mg^{2+} transporter or a regulator of Mg^{2+} transport is unclear [11]. However, *CNNM2* pathogenic mutations reduce its expression in the plasma membrane, resulting in defective Mg^{2+} reabsorption and Mg^{2+} wasting [11,38].

Furthermore, recent studies revealed that Mg^{2+} -ATP binding to the intracellular C-terminus of *CNNM2* is required for protein dimerization and Mg^{2+} efflux [41]. Disease-causing mutations that are located in the Mg^{2+} -ATP-binding site abolish ATP binding and Mg^{2+} efflux activity. The basis of the neurological defects remains unknown.

Group 2 hypomagnesemias

Bartter syndrome type 3

Bartter syndrome (BS) includes a group of several tubulopathies characterized by renal salt wasting, hypokalemia, hypochloremic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and low to normal blood pressure [42,43]. Patients usually present during the first years of life with failure to thrive, polyuria, and polydipsia. The main pathogenic mechanism in these tubulopathies is defective salt reabsorption predominantly in the TAL. Five different types of BS have been identified based on the gene involved [43]. Patients with BS type 3 or classic BS (OMIM #607364) develop hypomagnesemia during childhood or later in life [44]. This disorder is characterized by a great clinical variability, and there is a correlation between the severity of mutations and younger age at diagnosis [44,45].

BS type 3 is caused by recessive loss-of-function mutations of the *CLCNKB* gene, which encodes the kidney-specific Cl^- channel $ClC-Kb$ that is involved in $NaCl$ reabsorption in the renal tubule [6]. The $ClC-Kb$ protein is expressed in the basolateral membrane of epithelial cells in the TAL and the DCT. In these tubular segments, Cl^- exits the cell through $ClC-Ka$ and $ClC-Kb$ channels. Mutations in *CLCNKB* alter the intracellular Cl^- regulation, which subsequently interferes with the generation of the lumen-positive potential and results in salt wasting and possibly hypomag-

nesemia.

Gitelman syndrome

Gitelman syndrome (GS, OMIM #263800) is an autosomal recessive salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis, low or normal blood pressure, hypocalciuria, and hypomagnesemia with renal Mg^{2+} wasting [46]. GS is the most common cause of hereditary hypomagnesemia and is usually detected during adolescence or adulthood. GS may be asymptomatic or associated with mild symptoms including chronic fatigue, muscle weakness, thirst, salt craving, nocturia, and cramps, which can considerably reduce the quality of life [47]. Severe complications such as cardiac arrhythmias have been reported in some cases [46].

GS is caused by recessive inactivating mutations of the *SLC12A3* gene encoding the thiazide-sensitive NCC, which is localized in the apical membrane of DCT cells, where it plays a fundamental role in the reabsorption of Na^+ and Cl^- [48,49]. NCC mutations lead to reduced reabsorption, which results in Na^+ and Cl^- wasting, hypovolemia, and subsequent hyperaldosteronism with metabolic alkalosis [50]. The pathogenesis of hypocalciuria and hypomagnesemia may be explained by the compensatory paracellular reabsorption of Na^+ and Ca^{2+} in the PT due to volume reduction and by decreased apical expression of TRPM6 [51]. There is phenotypic variability in GS, including in patients with the same *SLC12A3* mutation.

Autosomal dominant hypocalcemia with hypercalciuria

Autosomal dominant hypocalcemia with hypercalciuria (ADHH, OMIM #601198) is a rare disorder of calcium homeostasis characterized by variable levels of hypocalcemia and low or normal serum levels of PTH [52]. Patients also present with hypomagnesemia, hypermagnesuria, hyperphosphatemia, and hypercalciuria [52,53]. Hypocalcemia is a derived effect of hypomagnesemia as a result of parathyroid failure or PTH resistance [30]. ADHH patients may develop hypocalcemic symptoms (paresthesias, carpopedal spasm, and seizures), and some have renal and basal ganglia calcifications, but others are asymptomatic [52].

ADHH is caused by heterozygous gain-of-function mutations in the *CASR* gene [52,54]. This gene encodes the

extracellular CaSR, a G protein-coupled receptor that is highly expressed in parathyroid glands and kidneys [53]. In the kidney, CaSR is highly expressed in the basolateral membrane of the TAL, where it regulates Ca²⁺ reabsorption independently of PTH [53,55]. A signaling pathway including two microRNAs and the tight junction proteins claudin-14 and claudin-16 mediates the effect of CaSR on renal Ca²⁺ and Mg²⁺ excretion [5]. Activating mutations of CaSR increase the expression of claudin-14, which binds to claudin-16 and blocks the cation permeability of the claudin-16/claudin-19 channel.

Episodic ataxia type 1

Loss-of-function mutations in the *KCNA1* gene are typically associated with an autosomal dominant neurological disorder called episodic ataxia type 1 (EA1, OMIM #160120), which is characterized by recurring episodes of ataxia and myokymia from early childhood [13]. The clinical phenotype in EA1 patients can include seizures, epilepsy, and, in some cases, paroxysmal kinesigenic dyskinesia, cataplexy, myokymia, and hypomagnesemia [56]. These symptoms can appear alone or in combination with EA1. A genotype-phenotype correlation analysis in a large cohort of EA1 patients revealed high inter- and intrafamilial variability of symptoms, but the penetrance of hypomagnesemia has not been evaluated [57].

The *KCNA1* gene encodes the α subunit of the voltage-gated potassium channel Kv1.1, which is abundantly expressed in specific neurons and plays an important role in regulating neuronal excitability in the central and peripheral nervous system [57]. In the kidney, *KCNA1* is exclusively expressed at the apical membrane of the DCT cells alongside the Mg²⁺ transporter TRPM6 [58]. Previous studies suggested that potassium (K⁺) secretion via Kv1.1 provides the electrochemical gradient needed for Mg²⁺ reabsorption by the TRPM6 channel [58,59]. Interestingly, two specific *KCNA1* heterozygous mutations, p.Asn255Asp and p.Leu328Val, have been associated with hypomagnesemia, leading to muscle cramps and tetanic episodes [58,59]. Electrophysiological analyses showed that both amino acid substitutions result in nonfunctional Kv1.1 channels [58–60]. The reduction in the K⁺ conductance depolarizes the apical membrane of DCT cells, reducing the electrical driving force and leading to renal Mg²⁺ loss. The frequency of hypomagnesemia in patients with *KCNA1* mutations may

be greater than reported, since serum Mg²⁺ levels have not been examined in all EA1 patients. Additional research is needed to understand the association of *KCNA1* mutations with hypomagnesemia.

Isolated dominant hypomagnesemia

Isolated dominant hypomagnesemia is a rare autosomal dominant disorder characterized by hypomagnesemia, hypocalciuria, and occasionally chondrocalcinosis (OMIM #154020) [61]. Some patients suffer from muscle cramps, episodes of convulsions, or chondrocalcinosis [61,62]. This disease has been identified in only three families who carry the same missense mutation, p.Gly41Arg, in the *FXKD2* gene and appear to be descendants of a common ancestor [62,63]. *FXKD2* encodes the kidney-specific regulatory γ -subunit of basolateral Na⁺, K⁺-ATPase, which is composed of a catalytic α subunit and an auxiliary β subunit. The Na⁺, K⁺-ATPase complex maintains the electrochemical gradients of Na⁺ and K⁺ across the basolateral plasma membrane that provide the driving force for transepithelial Mg²⁺ transport particularly in the DCT [15]. There are two splice variants of the γ -subunit: *FXKD2a*, which is expressed mainly in the TAL and PT, and *FXKD2b*, which is expressed exclusively in the basolateral membrane of the DCT and collecting duct [64]. Expression studies showed that the p.Gly41Arg mutation causes incorrect trafficking of the mutant γ *FXKD2b* subunit, preventing its interaction with the α and β Na⁺, K⁺-ATPase subunits [62]. This leads to destabilization and reduction of Na⁺, K⁺-ATPase activity in the DCT, which eventually results in decreased Mg²⁺ uptake and renal Mg²⁺ loss.

Hypomagnesemia, seizures, and mental retardation disorder type 2

Recently, three children from non-consanguineous families were reported who presented with generalized seizures in infancy associated with severe intellectual disability, massive renal Mg²⁺ wasting, and hypomagnesemia (HSMR type 2; OMIM #618314) [65]. Other findings included significant developmental delay and limited motor skills. Mutational analysis identified heterozygous *de novo* mutations in the *ATP1A1* gene encoding the catalytic $\alpha 1$ subunit of the Na⁺, K⁺-ATPase [65]. This ubiquitously expressed subunit is the major α isoform in the kidney and is present in practically

all cell types of the central nervous system [15]. Dominant and *de novo* mutations in *ATP1A1* are also the cause of autosomal dominant Charcot-Marie-Tooth disease type 2 (CMT2) [66]. To the best of our knowledge, serum Mg^{2+} levels have not been studied in CMT2 patients. Functional studies of the mutant Na^+ , K^+ -ATPase $\alpha 1$ subunits revealed loss of pump activity and anomalous cation permeability, leading to membrane depolarization [65]. These discoveries emphasize the essential task of the catalytic $\alpha 1$ subunit of the Na^+ , K^+ -ATPase in renal tubular Mg^{2+} transport and neuronal activity. Since *ATP1A1* is expressed in the TAL and DCT, it could affect transport in both tubular segments.

Epilepsy, ataxia, sensorineural deafness, and tubulopathy/seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance syndrome

Epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST) syndrome or seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME) syndrome (OMIM #612780) is an autosomal recessive disease characterized by early-onset epilepsy, delayed psychomotor development, ataxia, sensorineural deafness, and a salt-wasting tubulopathy with or without mental retardation [67,68]. The renal phenotype develops during the course of the disease and comprises polyuria, hypokalemia, metabolic alkalosis, hypocalciuria, and hypomagnesemia [69,70]. Plasma renin and aldosterone levels are increased and blood pressure is at the low end of the normal range. Urinary findings include K^+ , Mg^{2+} , and Na^+ wasting.

This complex disorder is caused by loss-of-function mutations in the *KCNJ10* gene encoding Kir4.1, one of the components of the inwardly rectifying K^+ channel Kir4.1/Kir5.1 [16,67,68]. *KCNJ10* is mainly expressed in glial cells of the brain, the stria vascularis of the inner ear, and the kidney [69]. The renal phenotype of patients with EAST/SeSAME syndrome closely resembles that of patients with GS, suggesting that *KCNJ10* mutations mainly impair transport in the DCT. In the kidney, Kir4.1 is expressed in the basolateral membrane of the DCT and is involved in K^+ recycling, which is needed for the activity of Na^+ , K^+ -ATPase, and generation of a negative transmembrane potential [16]. Mutations that inactivate Kir4.1 function lead to a depolarization of the basolateral membrane and to a reduction of the driv-

ing force for anion channels and Na^+ -coupled exchangers. This alteration in membrane voltage could also affect other transport processes, such as those for Cl^- and Mg^{2+} , which could explain the Mg^{2+} loss detected in patients with EAST/SeSAME syndrome.

Autosomal dominant tubulointerstitial kidney disease caused by *HNF1B* mutations

Autosomal dominant tubulointerstitial kidney disease (ADTKD) comprises a group of rare kidney disorders characterized by tubular damage and interstitial fibrosis without glomerular lesions [71]. Affected individuals usually develop CKD and end-stage renal disease in adulthood. Heterozygous mutations in several genes cause ADTKD, and this disease is subdivided into several subtypes based on the mutated gene [71].

ADTKD subtype *HNF1B* (ADTKD-*HNF1B*, OMIM #137920) is associated with hypomagnesemia [72,73]. The phenotypes detected in ADTKD-*HNF1B* patients are very heterogeneous and may appear during pregnancy, in childhood, or in adulthood [73]. Symptoms include renal cysts, kidney malformations, abnormalities of the genital tract and liver, and maturity-onset diabetes of the young (MODY) type 5 [72,74]. Hypomagnesemia and hypermagnesuria are observed in approximately 50% of patients [72,73].

ADTKD-*HNF1B* is caused by heterozygous mutations of the *HNF1B* gene, which encodes the developmentally regulated transcription factor hepatocyte nuclear factor-1 β (HNF1 β) [72,74,75]. These mutations are inherited in a dominant inheritance pattern or appear *de novo*. HNF1 β regulates tissue-specific gene expression in epithelial cells of several organs, including the kidneys, pancreas, liver, and urogenital tract [76]. In the adult kidney, HNF1 β is expressed in epithelial cells of all tubular segments. However, its role in renal Mg^{2+} reabsorption seems to take place in the DCT, since hypomagnesemia in ADTKD-*HNF1B* patients is frequently accompanied by hypocalciuria [72,73]. Several transcriptional targets of HNF1 β have been identified, including the *FXRD2* gene [72], which is involved in reabsorption of Mg^{2+} in the DCT, as described above. Therefore, inactivating mutations of HNF1 β would lead to reduced expression of *FXRD2* and, consequently, to renal Mg^{2+} wasting and hypomagnesemia [72]. HNF1 β also regulates the tran-

scription of *KCNJ10*, a gene that can affect Mg^{2+} transport in the DCT, as described above [77].

Transient neonatal hyperphenylalaninemia and primapterinuria

Transient neonatal hyperphenylalaninemia and primapterinuria (TNHP, OMIM #264070) is an autosomal recessive disorder characterized by mild transient hyperphenylalaninemia and elevated urinary levels of 7-biopterin [78]. Affected individuals are asymptomatic and exhibit normal psychomotor development. A follow-up study of TNHP patients showed that patients may also develop hypomagnesemia with renal Mg^{2+} wasting and MODY type diabetes [79]. TNHP is caused by mutations in the *PCBD1* gene, which encodes the bifunctional protein pterin-4 α -carbinolamine dehydratase (PCBD1). PCBD1 functions as a cytosolic enzyme that is implicated in the regeneration of the essential cofactor tetrahydrobiopterin as well as a coactivator of HNF1 β -mediated transcription within the nucleus [80]. Gene expression studies combined with immunohistochemical analysis showed that in the kidney, PCBD1 is expressed predominantly in the DCT [79]. PCBD1 interacts with the dimerization domain of HNF1 β and regulates the formation of a transcriptionally active tetrameric complex [81]. Binding of PCBD1 to HNF1 β stimulates the *FXYD2* promoter in the DCT, and *PCBD1* mutations identified in TNHP patients cause defective dimerization and degradation of the PCBD1 protein, leading to decreased *FXYD2* promoter activity [79]. The reduced expression of *FXYD2* would cause hypomagnesemia in these patients.

Kenny-Caffey syndrome type 2

Kenny-Caffey syndrome type 2 (KCS type 2, #OMIM 127000) is characterized by severe short stature, impaired skeletal development, eye abnormalities, hypomagnesemia, and hypoparathyroidism [82,83]. KCS type 2 patients may also have frequent episodes of low Ca^{2+} levels in serum triggered by hypoparathyroidism. This multisystem disease is caused by heterozygous missense mutations in the *FAM111A* gene, which encodes the nuclear trypsin-like serine protease FAM111A [82,83]. FAM111A is involved in the regulation of PTH production, calcium homeostasis, bone development

and growth, but the specific mechanisms have not been determined [82,83]. *FAM111A* mutations identified in patients usually appear *de novo*, but some cases with autosomal dominant inheritance have been described [84]. These mutations affect the peptidase domain of FAM111A and may impair its catalytic activity [83,85].

FAM111A, first identified as an antiviral restriction factor, is ubiquitously expressed, and its nuclear localization suggests that it might be involved in transcriptional regulation [82,83,86]. *FAM111A* mutations result in hyperactivation of the FAM111A intrinsic protease activity, which could cause abnormal degradation of DNA-binding proteins or FAM111A depletion through hyper-autoproteolytic cleavage [87–89]. Hyperactive FAM111A is cytotoxic, disrupting nuclear structure and pore distribution in a protease-dependent manner [89]. Targets of FAM111A protease activity have been recently identified and include nucleoporins and the associated germinal center-associated nuclear protein transcription/replication factor [89]. Hypomagnesemia in KCS type 2 patients could be attributed to degradation of transcription factors involved in magnesium homeostasis. Tan et al. [90] suggested a potential role of FAM111A in regulation of CaSR, since KCS type 2 shares phenotypic characteristics with ADHH-like hypocalcemia and hypoparathyroidism.

Group 3 hypomagnesemias

Mitochondria are abundant in kidneys, as the kidney requires high amounts of energy to enable the reabsorption of ions in different tubular segments [91]. Mitochondrial dysfunction leads to reduced ATP synthesis and loss of renal function. Because the function and biogenesis of mitochondria are under the genetic control of both mitochondrial DNA (mtDNA) and nuclear DNA, mutations in either genome can be the cause of disease [92]. mtDNA mutations are usually inherited from the patient's mother but they can also appear *de novo*. The clinical features of these patients can be very variable since they depend not only on the type of mutation but also on the number of mitochondria affected [92,93]. Mitochondrial diseases manifest in infancy and are multisystemic, and there are no effective treatment options for the patients. Some mitochondrial diseases are associated with hypomagnesemia but the mechanism under-

lying how they cause hypomagnesemia remains unsolved. These diseases may affect the TAL, the DCT, or both.

Hypertension, hypercholesterolemia, and hypomagnesemia

This disorder was identified in a large pedigree and includes hypertension, hypercholesterolemia, and hypomagnesemia (OMIM #500005) [94]. Affected individuals also have hypocalciuria and hypokalemia. Each of these traits was transmitted via the maternal lineage with a pattern indicating mitochondrial inheritance. Other clinical characteristics include migraine headache, sensorineural hearing loss, and hypertrophic cardiomyopathy, all usually associated with mitochondrial dysfunction. Sequence analysis of the mitochondrial genome in the maternal lineage of the pedigree identified a C to T transition in the *MT-TI* gene, which encodes isoleucine transfer RNA (tRNA^{Ile}) [94]. Further analysis of affected members revealed that all copies of the mtDNA contain this mutation. The affected C is located immediately 5' to the tRNA^{Ile} anticodon, and biochemical studies showed that the substitution of T significantly weakens ribosome binding [95]. These studies suggest that this mutation results in the loss of mitochondrial function. Hypomagnesemia associated with hypocalciuria points to a primary defect in the DCT [96].

Kearns-Sayre syndrome

Kearns-Sayre syndrome (KSS, OMIM #530000) is a rare progressive multisystem disease characterized by ophthalmoparesis/ptosis and pigmentary retinopathy. The onset is typically before 20 years of age, and patients typically present one of the following: cerebellar ataxia, cardiac conduction defects, deafness, short stature, cognitive involvement, tremor, and cardiomyopathy [97]. Some cases develop hypoparathyroidism and renal tubular dysfunction resulting in severe hypomagnesemia, hypocalcemia with hypermagnesuria, and hypokalemia [98,99]. KSS is caused by large deletions in mtDNA, which can reduce considerably ATP production [93]. In most cases, the deletions arise *de novo* but some are transmitted through maternal inheritance. Patients' cells usually contain a mixture of wild-type and mutant mtDNA molecules in variable quantities, which is critical in determining the level of cellular dysfunction [92]. A defect in Mg²⁺ reabsorption in the TAL or DCT, due to ATP

depletion, could be the cause of hypomagnesemia in these patients.

Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis syndrome

Hyperuricemia, pulmonary hypertension, renal failure and alkalosis (HUPRA) syndrome (OMIM #613845) is an autosomal recessive disease characterized by early-onset progressive renal failure, hyperuricemia, metabolic alkalosis, pulmonary hypertension, developmental delay, and, in some cases, hypomagnesemia [100]. This rare disorder has been diagnosed in only six children from three families and it is caused by homozygous missense mutation in *SARS2* on chromosome 19, which encodes the mitochondrial seryl-tRNA synthetase (SARS2) [100,101]. SARS2 catalyzes the serine aminoacylation of two mitochondrial tRNAs. Only two mutations have been identified in patients with HUPRA syndrome, p.Asp390Gly and p.Arg402His. The p.Asp390Gly mutation significantly reduces the aminoacylation of one mitochondrial tRNA leading to its degradation, which would cause alterations in the synthesis of mitochondrial proteins and consequently in energy supply [100]. Decreased energy production may account for diminished Na⁺, K⁺-ATPase activity in the TAL and DCT, which could explain the salt wasting and hypomagnesemia observed in HUPRA patients.

Concluding remarks

Mg²⁺ is an essential ion that plays a key role in the regulation of many cellular functions. In the kidney, proteins expressed in the apical and basolateral membranes of the TAL and DCT maintain serum Mg²⁺ levels within a narrow physiological range. Mutations in the genes that encode these proteins cause different types of hypomagnesemia. Consequently, serum Mg²⁺ levels should be determined in patients presenting with seizures, muscle cramps, and arrhythmias.

In this review, we have described the current research findings on hereditary hypomagnesemias. Some of these diseases share common characteristics and thus precise diagnosis requires the identification of the causative mutation. Therefore, we suggest a diagnostic approach for clinicians based on previously reported data [2,102] (Fig. 4). Many questions are

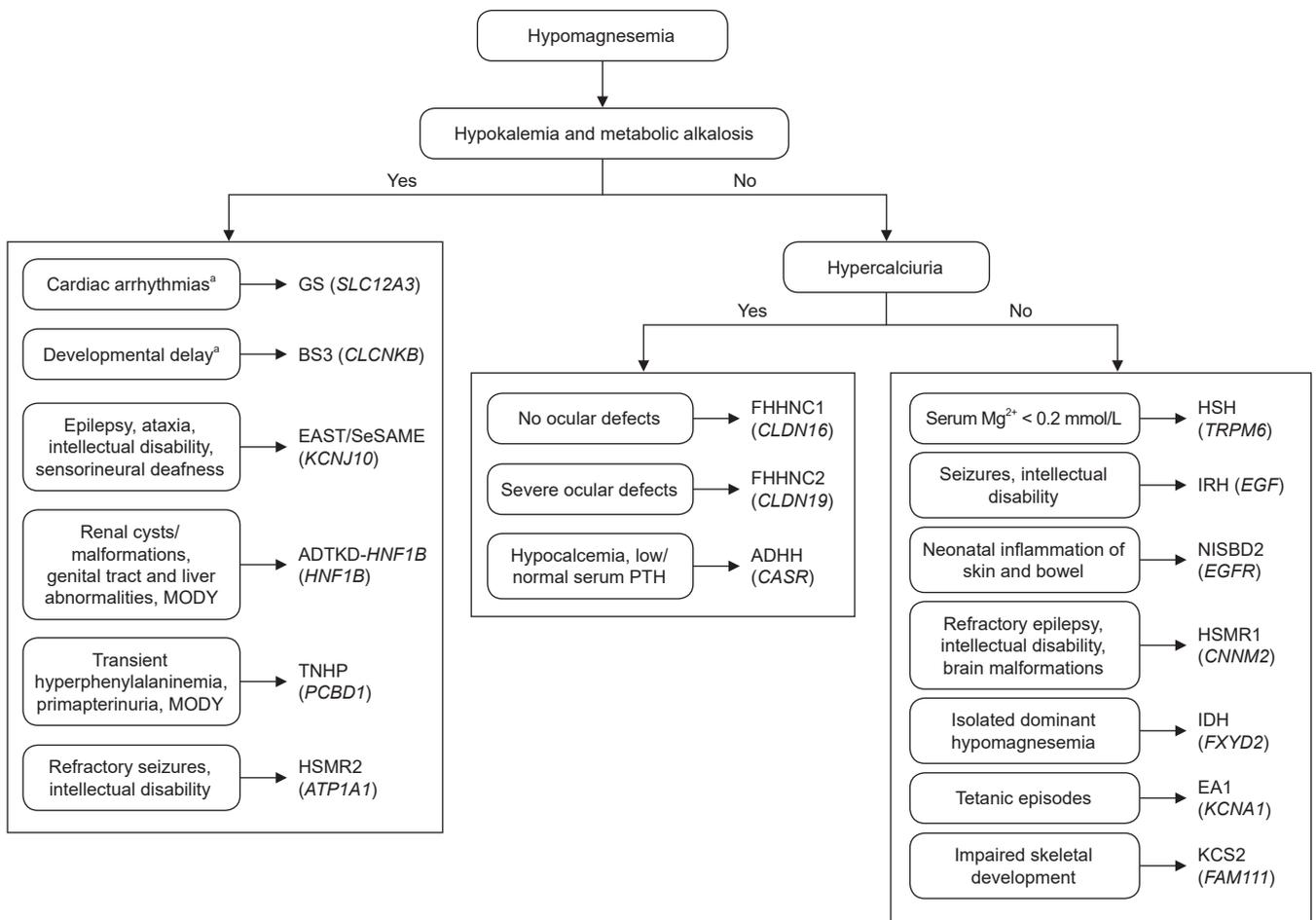


Figure 4. Flowchart for the diagnosis of inherited hypomagnesemias. Group 3 hypomagnesemias were not included because the clinical features of these patients are extremely variable.

ADHH, autosomal dominant hypocalcemia with hypercalciuria; ADTKD-*HNF1B*, autosomal dominant tubulointerstitial kidney disease subtype *HNF1B*; BS3, Bartter syndrome type 3; EA1, episodic ataxia type 1; EAST, epilepsy, ataxia, sensorineural deafness, and tubulopathy; FHHNC1, familial hypomagnesemia with hypercalciuria and nephrocalcinosis type 1; FHHNC2, familial hypomagnesemia with hypercalciuria and nephrocalcinosis type 2; GS, Gitelman syndrome; HNF1B, hepatocyte nuclear factor-1 beta; HSH, hypomagnesemia with secondary hypocalcemia; HSMR1, hypomagnesemia, seizure, and mental retardation disorder type 1; HSMR2, hypomagnesemia, seizures, and mental retardation disorder type 2; IDH, isolated dominant hypomagnesemia; IRH, isolated recessive hypomagnesemia; KCS2, Kenny-Caffey syndrome type 2; MODY, maturity-onset diabetes of the young; NISBD2, neonatal inflammatory skin and bowel disease type 2; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance; TNHP, transient neonatal hyperphenylalaninemia and primapterinuria.

^aThese clinical signs do not appear in all patients.

still unanswered. For instance, the underlying mechanisms for hypomagnesemia in most hereditary diseases are still unclear. In addition, the physiological functions of *CNNM2* and *SLC41A1* remain to be clarified. The identification of the protein(s) that facilitate the basolateral extrusion of Mg^{2+} will greatly improve our understanding of Mg^{2+} transport in the DCT. A better knowledge of the pathophysiology of these diseases is needed to develop specific therapeutic

strategies. So far, the only therapeutic option to treat hypomagnesemia in patients with GS, BS type 3, EAST/SeSAME, HSH, or isolated dominant hypomagnesemia is essentially supportive and involves oral or intravenous magnesium supplementation. However, this approach has been found to be unsuccessful in patients with other hypomagnesemias like FHHNC, HSMR, and ADTKD-*HNF1B*.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Disclosure

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