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Clinical and genetic approach to renal hypomagnesemia

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ABSTRACT

Magnesium (Mg²⁺) is an important intracellular cation and essential to maintain cell function including cell proliferation, immunity, cellular energy metabolism, protein and nucleic acid synthesis, and regulation of ion channels. Consequences of hypomagnesemia affecting multiple organs can be in overt or subtle presentations. Besides detailed history and complete physical examination, the assessment of urinary Mg²⁺ excretion is helpful to differentiate renal from extra-renal (gastrointestinal, tissue sequestration, and shifting) causes of hypomagnesemia. Renal hypomagnesemia can be caused by an increased glomerular filtration and impaired reabsorption in proximal tubular cells, thick ascending limb of the loop of Henle or distal convoluted tubules. A combination of renal Mg²⁺ wasting, familial history, age of onset, associated features, and exclusion of acquired etiologies point to inherited forms of renal hypomagnesemia. Based on clinical phenotypes, its definite genetic diagnosis can be simply grouped into specific, uncertain, and unknown gene mutations with a priority of genetic approach methods. An unequivocal molecular diagnosis could allow for prediction of clinical outcome, providing genetic counseling, avoiding unnecessary studies or interventions, and possibly uncovering the pathogenic mechanism. Given numerous identified genes responsible for Mg²⁺ transport in renal hypomagnesemia over the past two decades, several potential and specific molecular and cellular therapeutic strategies to correct hypomagnesemia are promising.

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Magnesium (Mg$^{2+}$), the second-most abundant intracellular cation, is pivotal as a cofactor in the maintenance of numerous cell functions. Deficiency of Mg$^{2+}$ can lead to muscle weakness, tremor, seizure, arrhythmia, coma, and even death [1,2]. Up to 15% of hospitalized patients and 60% of patients admitted to intensive care unit have hypomagnesemia [3–5]. Gastrointestinal and renal losses are the two major causes of hypomagnesemia. The acquired renal hypomagnesemia commonly results from medications, alcohol, and osmotic diuresis. Inherited renal hypomagnesemia is defined as hypomagnesemia in which Mg$^{2+}$ is absorbed [2]. Specifically, the inherited renal hypomagnesemia features more variable in characteristics, more refractory in treatment and more severe in consequence. Without timely recognition and appropriate treatment, it can lead to severe complications such as cardiac arrhythmias and death.

Numerous genes encoding proteins involved in Mg$^{2+}$ transport in the renal tubules have been identified over the last two decades. Such newfound knowledge can potentially enable us to modify and personalize therapeutic strategies. Our aim is to summarize the molecular advances that are linked to renal hypomagnesemia and propose a comprehensive molecular approach for diagnosis and management. Recent advances in molecular and cellular therapies of inherited disorders are also discussed.

**Magnesium homeostasis**

Magnesium (Mg$^{2+}$) is a crucial cation involved in a number of biological processes, including cell proliferation, immunity, cellular energy metabolism, protein and nucleic acid synthesis, and regulation of ion channels [1,2]. The serum Mg$^{2+}$ is tightly maintained within a narrow range. In the body, around 53% are distributed and stored in bones, 27% in muscles, 19% in soft tissues, and only 1% in blood. Around 65–70% of the circulating Mg$^{2+}$ is in the ionized form which is the active form critical for physiological function. The rest of Mg$^{2+}$ binds with either proteins or anion such as citrate and phosphate. The extracellular Mg$^{2+}$ concentration is tightly regulated by gut and kidney, and the serum Mg$^{2+}$ level reflects the equilibrium between absorption in intestine and urinary excretion.

**Gastrointestinal absorption of Mg$^{2+}$**

Mg$^{2+}$ is acquired through daily food intake, where nearly 35%–80% of the ingested Mg$^{2+}$ is absorbed [2]. Specifically, around 30–50% of dietary Mg$^{2+}$ intake is absorbed in the jejunum and ileum by way of passive paracellular route and in the colon through active transcellular route by transient receptor potential melastatin type 6 and 7 (TRPM6 and 7). The absorbed Mg$^{2+}$ enters the bloodstream by CNNM4 and Na$^{+}$-Mg$^{2+}$ exchanger at the basolateral side of cells [6].

**Renal regulation of Mg$^{2+}$ reabsorption**

Serum Mg$^{2+}$ is subsequently excreted in the urine after storage in organs and cellular utilization. The kidney determines the final urinary Mg$^{2+}$ excretion, and hence plays a major role in Mg$^{2+}$ homeostasis. In the kidney, only 3–5% of filtered Mg$^{2+}$ is excreted after reabsorption in renal tubules. As shown in Fig. 1, around 15–25% of filtered Mg$^{2+}$ is absorbed in the PCT via paracellular pathway. The increasing intratubular Mg$^{2+}$ concentration triggers the passive reabsorption via claudin 1 and 2 in the late PCT [7,8]. Schlingmann et al. identified children with biallelic variants in KCNJ16, which encodes basolateral potassium channel (Kir5.1) of PCT and DCT, have hypokalemic tubulopathy, salt wasting, disturbed acid-base homeostasis, sensorineural deafness, and hypomagnesemia [9]. In the TALH, about 60–70% of filtered Mg$^{2+}$ is reclaimed passively by paracellular pathway via claudin 16 and 19 triggered by positive luminal transepithelial voltage. This positive intraluminal voltage is generated by apical Na$^{+}$-K$^{+}$-Cl$^{-}$ cotransporter (NKCC2)-mediated Na$^{+}$, K$^{+}$, Cl$^{-}$ reabsorption, and apical renal outer medullary potassium (ROMK)-mediated parallel K$^{+}$-excretion [10–13]. Calcium-sensing receptor (CaSR) expressed abundantly in basolateral side of TALH regulates paracellular Mg$^{2+}$ reabsorption by involving the regulation of salt reabsorption in TAL and the expression of claudin-14 [14,15]. Recent study has shown that children with heterozygous variants in RRAGD, which encodes GTPase RagD of TALH and DCT, has hypomagnesemia, salt wasting, nephrocalcinosis, and dilated cardiomyopathy [16]. The RagD variants leads to constitutive activation of mTOR signaling in vitro and is supposed to interfere with the handling of Mg$^{2+}$ and other electrolytes in TALH and DCT. Although the amount of reabsorbed Mg$^{2+}$ in distal convoluted tube (DCT) is lower than that in PCT and TALH, the DCT plays a crucial role of determining final urinary Mg$^{2+}$ excretion. The active reabsorption of 5–10% of filtered Mg$^{2+}$ is tightly regulated in the DCT through transcellular TRPM6 [Fig. 1]. Genetic defects of TRPM6 encoding TRPM6 result in renal Mg$^{2+}$ wasting and consecutive hypoparathyroidism and hypocalcemia (HS). The mutations of SLC12A3 encoding thiazide-sensitive sodium chloride cotransporter (NCC) in DCT lead to Na$^{+}$, K$^{+}$, and Cl$^{-}$ wasting, and reduced expression of TRPM6 [17]. Kv1.1, the apical voltage-gated potassium channel, has been demonstrated to be involved in Mg$^{2+}$ reabsorption, by the finding that non-functional Kv1.1 results in isolated hypomagnesemia [18]. Kv1.1 facilitates Mg$^{2+}$ reabsorption by generation of intraluminal positive voltage through apical secretion of potassium in DCT. The binding of epidermal growth factor (EGF) and EGF receptor in the basolateral side of DCT regulates the apical shutting of TRPM6, and defects in EGF gene have been reported to cause isolated recessive hypomagnesemia, where apical TRPM6 expression is reduced [14,19]. The γ-subunit of the basolateral Na$^{+}$-K$^{+}$ ATPase encoded by FXYD2 stabilizes Na$^{+}$-K$^{+}$ ATPase. Mutations in FXYD2 have been demonstrated to cause diminished NCC activity and reduced driving force of Mg$^{2+}$ reabsorption via TRPM6 [20]. The α1-subunit encoded by
ATP1A1 represents the exclusive of α-subunits of basolateral Na⁺-K⁺-ATPase in kidney [21]. Heterozygous mutations in ATP1A1 recently have been reported to cause renal hypomagnesemia, seizure, and mental retardation [22]. The hepatocyte nuclear factor 1 (HNF1b) and pterin-4a-carbinolamine dehydratase (PCBD1), the transcriptional regulatory proteins of γ-subunit of the basolateral Na⁺-K⁺-ATPase, have been reported to be associated with renal Mg²⁺ wasting, and mutations in HNF1B and PCBD1 lead to inherited dominant hypomagnesemia [15,23]. The basolateral Na⁺-K⁺-ATPase establishes the transapical membrane gradient critical for activity of TRPM6. The transcriptional factors including HNF1β and PCBD1 of γ-subunit of Na⁺-K⁺-ATPase, encoded by FXYD2, regulate Mg²⁺ reabsorption via alteration expression of γ-subunit of Na⁺-K⁺-ATPase. Kv4.1 located on basolateral side recycles the imported by Na⁺-K⁺-ATPase via conducting outward K⁺ currents. The paracrine action of EGF regulates the activity of TRPM6. The Mg²⁺ efflux is conducted in Na⁺-Mg²⁺ exchanger and possibly also in CNNM2.

Clinical manifestations of hypomagnesemia

Hypomagnesemia is defined as total serum Mg²⁺ concentration less than 1.7 mg/dL (0.7 mM), and the clinical symptoms of hypomagnesemia may not be significant unless it reaches profound hypomagnesemia below 1.2 mg/dL (0.5 mM). Since Mg²⁺ is involved in many vital physiological functions hypomagnesemia may cause a myriad of manifestations involving multiple organs [Fig. 2]. Neuronal Mg²⁺ involved in the regulation of N-methyl-D-aspartate (NDMA) and γ-aminobutyric acid (GABA) receptor, and deficiency of Mg²⁺ leads to hyperexcitability of NMDA and decreased stimulation of GABA [28,29]. In the central nervous system, as shown in Fig. 2, hypomagnesemia can cause tremor and convulsion from neuromuscular hyperexcitability and it is also associated with...
migraine, brain injury, stroke, and mood disorders [30–32]. In lung, Mg\(^{2+}\) has bronchodilatory and anti-inflammatory effects on airway [33,34]. Hypomagnesaemia has been shown to be associated with asthma and chronic obstructive pulmonary disorder, therefore, Mg\(^{2+}\) is supposed to have therapeutic roles on these disorders. In cardiovascular system, Mg\(^{2+}\) regulates the myocardial contractility and has effects of anti-inflammation, vasodilatation, and inhibitory crystallization of calcium-phosphate [35,36]. Hence, hypomagnesemia may cause arrhythmia, myocardial infarction, vascular calcification, hypertension, and coronary artery diseases. In muscle, Mg\(^{2+}\) acts as Ca\(^{2+}\) antagonist to compete the binding sites of proteins responsible for muscle contraction [37]. Hence, Mg\(^{2+}\) deficiency may lead to hypercontractibility and muscle cramps. In bone, Mg\(^{2+}\) participates in bone formation by stimulating the proliferation of osteoblast and increasing the

Fig. 2 Pathophysiology of hypomagnesemia. (A) Clinical manifestations and organ-specific consequences of hypomagnesemia. (B) Cellular physiology of Mg\(^{2+}\). Several transporters are responsible for the cellular Mg\(^{2+}\) homeostasis. Mg\(^{2+}\) stabilizes the structures of DNA and RNA, DNA and RNA polymerases, and their repair in the nucleus. Additionally, Mg\(^{2+}\) also regulated the cell growth and proliferation. In cytosol, Mg\(^{2+}\) is involved in many enzymatic reactions and regulates the glycolysis and ATP synthesis.
solubility of minerals. Mg\(^{2+}\) deficiency has been reported to be associated with osteoporosis [38]. Mg\(^{2+}\) may have effects on the secretion of insulin by the findings that patients with Mg\(^{2+}\) deficiency have a decreased insulin secretion [39]. Additionally, patients with diabetes also have low serum Mg\(^{2+}\) levels [40]. In liver, patients with liver cirrhosis and fatty liver are Mg\(^{2+}\) depleted. This may be due to enzymatic reactions in liver that are Mg\(^{2+}\)-dependent [41]. Mg\(^{2+}\) has been reported to regulate the proliferation and development of T lymphocytes, and it is associated with X-linked T-cell immunodeficiency [1,42].

Approach to hypomagnesemia

Apart from inadequate dietary intake and malabsorption in gut, defects of renal reabsorption are largely responsible for the dysregulation of Mg\(^{2+}\) homeostasis. In general, causes of hypomagnesemia can be divided into two categories: high renal Mg\(^{2+}\) excretion and low renal Mg\(^{2+}\) excretion including gastrointestinal, tissue sequestration, and shifting origins. Besides detailed medical and family histories, complete physical examination, and urine and serum electrolytes measurement, fractional excretion rate of Mg\(^{2+}\) (FEMg) can provide a rapid differentiation of these two categories [Fig. 3]. In the setting of hypomagnesemia, FEMg >4% indicates renal Mg\(^{2+}\) wasting, while FEMg <2% suggests appropriate renal Mg\(^{2+}\) conservation and Mg\(^{2+}\) wasting of extra-renal origin. Of note, a low glomerular filtration rate may reduce the filtered load of Mg\(^{2+}\), and therefore lowers the cutoff values of FEMg indicating renal wasting. Common causes of gastrointestinal Mg\(^{2+}\) losses include dietary deprivation, diarrhea, malabsorption, use of proton pump inhibitor, and rare primary familial hypomagnesemia caused by molecular defects in TRPM6. Acute pancreatitis, massive blood transfusion, hungry bone syndrome, refeeding syndrome, and cardiopulmonary bypass are common causes of hypomagnesemia secondary to cellular shift and tissue sequestration. Rarely, in hypervolemia and/or overall reduction of serum anion, FEMg may still appear appropriate, despite an overall increase in renal Mg\(^{2+}\) excretion. Renal hypomagnesemia can be caused by an increased glomerular filtration and defective transport in proximal tubular segments, thickening ascending limb of the loop of Henle or distal convoluted tubules.

Identify genetic forms of renal hypomagnesemia

Before establishing the diagnosis of inherited renal hypomagnesemia, the acquired etiologies of renal Mg\(^{2+}\) wasting such as medications should be carefully excluded. Historical clues such as prior hypomagnesemia, associated organ abnormalities in family members, use of drugs affecting hypomagnesemia-loop diuretics, proton pump inhibitor, calcineurin inhibitor, aminoglycoside, foscarnet, cisplatin and cetuximab, age of onset, and nephrolithiasis or nephrocalcinosis must be carefully obtained. The diagnosis of inherited renal hypomagnesemia would be made after exclusion the acquired etiologies above-mentioned.

Differential diagnosis of inherited renal hypomagnesemia

The mode of inheritance, assessment of urine and blood biochemistry studies, presence of extra-renal symptoms all

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Fig. 3 Congenital and acquired causes of hypomagnesemia.
aid in determination of further genetic testing. The models of inheritance of inherited renal hypomagnesemia include autosomal dominant, autosomal recessive and maternal inheritance. As shown in Fig. 4, the etiology of inherited renal hypomagnesemia can be divided into lesions in TALH, DCT and PCT by renal calcium excretion. Hypercalciuria points the TALH tubulopathy such as Bartter syndrome, autosomal dominant hypocalcemia, and familial hypercalciuria hypomagnesemia nephrocalcinosis. Absence of hypercalciuria can be further divided into lesions in DCT and PCT. The presence of hypokalemia is cardinal feature for differentiating the Gitelman syndrome-like hypomagnesemia from others DCT tubulopathy [Fig. 4]. Gitelman syndrome-like hypomagnesemia can be further differentiated by the presence of extrarenal manifestations and modes of inheritance. Finally, mitochondrial hypomagnesemia is one of important causes of PCT tubulopathy.

Genetic approach to inherited renal hypomagnesemia

As shown in Fig. 5, direct Sanger sequencing can identify the disease-specific gene assessed by above-mentioned approach [Table 1 and Fig. 4]. Of note, direct Sanger sequencing will miss deep intronic mutation not rare in Gitelman syndrome and large deletion including cBS, familial hypomagnesemia hypercalciuria nephrocalcinosis, HNF1b nephropathy, hypomagnesemia secondary hypocalcemia, and EAST syndrome [43,44]. Therefore, if unable to identify the causative genetic mutation, analysis of deep intronic mutation or MLPA (multiplex ligation-dependent probe amplification) for large deletion may be warranted. In patients of diseases with uncertain gene due to the overlapping phenotype and genetic heterogeneity, a gene panel can be considered to assess multiple causal genes simultaneously. The gene panel is also recommended for patients of suspicion of specific disease without detected variants by direct Sanger sequencing. Some patients might have no detected variants by direct Sanger sequence, MLPA, cDNA, and gene panels. In such cases, next generation sequencing (NGS) will aid in the molecular diagnosis. NGS, such as whole exome sequencing (WES) and whole genome sequencing (WGS), provide rapid screen of known genes, as well as modifier genes and epigenetic modification. The bioinformatics analysis and variants databases are essential for determining the pathogenic role of variants identified by NGS. Epigenetic analysis, including DNA methylation, siRNA regulation, and chromatin immunoprecipitation sequencing, may be the further potential tests for patients without identified variants by NGS.

Management of hypomagnesemia

Delivery of Mg\(^{2+}\) supplementation, avoidance of exacerbated renal Mg\(^{2+}\) wasting, and correction of accompanying metabolic disarrangement is the mainstay treatment in inherited renal hypomagnesemia. The route of administration and dosage of Mg\(^{2+}\) supplement dependents on the severity of hypomagnesemia. In patients with acute symptomatic hypomagnesemia, parenteral Mg\(^{2+}\) supplementation should be considered for alleviating potential complications. Oral Mg\(^{2+}\) supplementation is suitable for patients with non-acute and asymptomatic hypomagnesemia. The common formulations of Mg\(^{2+}\) supplemnetations and Mg\(^{2+}\)-rich food are summarized in Table 2. Although there is no upper limit of dietary Mg\(^{2+}\), oral elemental Mg\(^{2+}\) supplementation less than 350 mg
per day is safe for adults and children older than 8 years [45]. The tolerable upper limit of daily elemental Mg$^{2+}$ supplementation for children 1–3 years and 4–8 years are 65 mg and 110 mg, respectively [46]. Based on the different bioavailability of Mg$^{2+}$ formula, organic Mg$^{2+}$ compounds including Mg$^{2+}$ citrate, Mg$^{2+}$ aspartate, Mg$^{2+}$ chloride, and Mg$^{2+}$ glycerophosphate are superior to Mg$^{2+}$ oxide and Mg$^{2+}$ sulfate in correcting hypomagnesemia [47]. Conditions associated with renal hyperfiltration (osmotic diuresis, poor control of hyperglycemia, and massive fluid intake) and increased filterable Mg$^{2+}$ (loop diuretics, chronic metabolic acidosis, low serum anion including hypoalbuminemia, hypophosphatemia) could aggravate the renal Mg$^{2+}$ wasting and should be corrected appropriately. Accordingly, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) that reduce glomerular filtration can be considered for patients who are in a glomerular hyperfiltrative state. In addition, aldosterone antagonist has been reported to ameliorate the renal Mg$^{2+}$ wasting and maintain serum Mg$^{2+}$ levels in patients with congestive heart failure [48]. Aldosterone has been demonstrated to induce renal Mg$^{2+}$ wasting through increases in intracellular Mg$^{2+}$ shifts from muscle and bone [49]. Additionally, aldosterone has also been shown to downregulate the activity of renal TRPM6 [50]. Several metabolic disarrangements including hypokalemia, hypocalcemia, hypercalciuria, and hyperglycemia caused by diabetes mellitus may also occur in patients with inherited hypomagnesemia. The condition of hyperglycemia could further exacerbate hypomagnesemia. Hypocalcemia, hypokalemia and hypercalciuria may further deteriorate renal function if left untreated. Therefore, these accompanied metabolic disarrangements should be addressed simultaneously.

**Potential therapy for genetic renal hypomagnesemia**

As shown in Fig. 6, molecular therapies that target modifications at the level of DNA, RNA, and proteins are currently being developed and applied on variety of inherited diseases. Successful development of personalized treatment approaches is dependent on the severity of diseases, identification of genetic defects, and understanding the pathophysiological mechanism [34–47]. DNA therapies include gene replacement therapy and genomic editing [51,52]. Gene replacement therapy works by using the therapeutic vectors to insert the normal copy of mutant gene into host cells, and this might be potential for patients with large deletion mutation. Heikkinen et al. succeeded in delivering the COL4A5 gene by adenoviral vector to glomerular cells [53]. Genomic editing allows for precise editing of genomic DNA in vivo or ex vivo by utilizing CRISPR/Cas system and EFNs and TALENs [54,55]. Daga et al. developed two-plasmid approach to achieve a stable variant-specific correction in the X-linked COL4A5 (p.Gly624Asp) and COL4A3 gene (p.Gly856Glu) using CRISP/Cas9 genome editing [56]. RNA therapies are represented by splicing modulation, RNA silence, and RNA editing. The splicing modulation is conducted for correcting aberrant splicing by antisense oligonucleotides, U1 splicesosomal RNA, or trans-splicing [57–59]. As shown in Table 1, splice site
Table 1 Clinical, biochemical, and genetic characteristics of inherited disorders of renal hypomagnesemia.

| Disorders | Involved tubule | Inheritance | Gene | Protein | Large deletion | Age at onset | Serum Ca | Serum K | Blood pH | Urine Mg | Urine Ca | Extrarenal manifestation | Nephrocalcinosis/ nephrolithiasis | Renal anomaly | Early ESRD | Reference |
|-----------|----------------|-------------|------|---------|----------------|-------------|---------|---------|---------|---------|---------|------------------------|-------------------------|--------------|------------|-----------|
| ADH       | TALH           | AD          | CASR | CaSR    | Yes            | Adolescence/ adulthood | –         | –       | ↓       | ↑       | ↑       | ↓                     | Yes                      | No           | No         | [65]      |
| FHHNC     | TALH           | AR          | CLDN16 | Claudin-16 | Yes        | Childhood/ adolescence | –         | –       | ↑       | ↓       | ↑       | ↑                     | Yes                      | No           | Yes        | [66–69]   |
| CBS       | TALH            | AR          | CLCNKB | CIC-Kb  | Yes            | Childhood | var.     | ↓       | ↑       | ↓       | –       | –                     | No                      | Yes          | (infrequent)| [70–73]   |
| BS, type IVa | TALH          | AR          | BSND  | Barttin | Yes            | Infancy    | var.     | ↓       | ↑       | ↓       | –       | –                     | Sensoryneural deafness | Yes          | No         | [74]      |
| BS, type IVb | TALH          | AR          | CLCNKA | Claudin-16 | Yes        | Infancy     | var.     | ↓       | ↑       | ↓       | –       | –                     | Sensoryneural deafness | Yes          | No         | [75,76]   |
| EKCA syndrome | TALH, DCT     | No          | RAGD  | No       | No            | Infancy/ Childhood | –         | ↓       | ↑       | ↑       | ↑ or ↓  | ↓                     | Yes                      | No           | No         | [77]      |
| HNF1B nephropathy | DCT | No          | HNF1B | HNF1beta | Yes | Adolescence/ adulthood | –         | ?       | ?       | – or ↑  | – or ↓  | ↓                     | MODY                     | No           | Yes        | [78–81]   |
| EAST syndrome | DCT         | AR          | KCN4.1 | Yes       | Neonate/ infancy | –         | ↓       | ↑       | ↑       | ↑       | ↓                     | Epilepsy                  | No           | No         | [82,83]   |
| HPABH4D  | DCT            | AR          | PCBD1 | PCBD1   | Yes            | Adolescence/ adulthood | –         | –       | –       | ?       | ↑       | –                     | MODY                     | No           | No         | [79,80]   |
| GS        | DCT            | AR          | SLC2A3 | NCC     | Yes            | Adolescence/ adulthood | –         | ↓       | ↑       | ↑       | ↓       | –                     | Chondrocalcinosis     | No           | No         | [81,84–89]|
| IDH       | DCT            | AD          | FXYD2  | γ subunit of Na+K+ ATPase | No     | Adolescence/ adulthood | –         | –       | –       | – or ↑  | – or ↓  | ↓                     | No                      | No           | No         | [85]      |
| HSMR syndrome 2 | DCT      | AD          | ATP1A1 | Yes       | Neonate/ infancy | –         | ↓       | ↑       | ↑       | ↑       | ↓                     | Intellectual disability, epilepsy | Yes          | No         | [22]      |
| HSMR syndrome 1 | DCT | AD/AR       | CNM2  | Yes       | Infancy/ childhood | –         | –       | –       | – or ↑  | –       | –                     | Intellectual disability, epilepsy, impaired skeletal development, hypocalcemia, hypoparathyroidism | No           | No         | [91]      |
| KCN2 syndrome | DCT      | AD          | FAM11I1A | FAM11A | No | Infancy | –         | –       | – or ↑  | –       | –       | –                     | RENAL INSUFFICIENCY     | No           | No         | [92,93]   |
| EA1       | DCT            | AD          | KCNA1 | Kv1.1    | No            | Childhood    | –         | –       | ?       | – or ↓  | –       | –                     | Intellectual disability, epilepsy | No           | No         | No        | [94]      |
| HSH       | DCT            | AR          | TRPM6  | TRPM6    | Yes            | Infancy    | –         | –       | – or ↑  | –       | – or ↑  | –                     | Severe inflammation of skin and bowel heart abnormalities | No           | No         | No        | [95,96]   |
| IRE       | DCT            | AR          | EGF    | No       | No            | Infancy    | –         | –       | – or ↑  | –       | –       | –                     | Renal dysplasia         | No           | No         | [97]      |
| NSBD2     | DCT            | AR          | EGFR   | No       | No            | Infancy    | –         | –       | – or ↑  | –       | –       | –                     | Severe inflammation of skin and bowel heart abnormalities | No           | No         | No        | No        | [98]      |
| GS phenocopy | DCT | No          | MT-7I, MT-7F MT-7I, MT-7F | No       | Adulthood | –         | ↓       | – or ↑  | ↑       | ↑       | ↓                     | No                      | No           | No         | [99]      |

(continued on next page)
| Disorders Involved tubule | Inheritance | Gene | Protein | Large deletion | Age at onset | Serum Ca | Serum K | Blood pH | Urine Mg | Urine Ca | Extrarenal manifestation | Nephrocalcinosis/ nephrolithiasis | Renal anomaly | Early ESRD |
|--------------------------|-------------|------|---------|---------------|-------------|---------|--------|---------|---------|---------|--------------------------|-----------------------------|--------------|-----------|
| HUPRA syndrome | PCT | AR | SAS2 | SAS2 | No | Infancy | ↓ | ↑ | ↑ | ↓ | ↑ | Hyperuricemia, elevated serum lactate, pulmonary hypertension, prematurity, intellectual disability, diabetes mellitus | No | No | Yes | [106] |
| KSS | PCT | Mt | Mitochondrial deletion | Yes | Childhood | ↓ | ↓ | ↓ or ↑ | ↑ | ↑ | Brain, eye, ear involvement. Muscle weakness, ataxia, intellectual disability, epilepsy, diabetes mellitus, gonadal failure, thyroid disease, hypoparathyroidism | No | No | No | [101–103] |
| Hypokalemic tubulopathy, DCT salt wasting, disturbed acid-base homeostasis and deafness | PCT TALH | AR | KCN1/6 | KCN1/6 | No | Infancy/ Childhood | ↓ | ↑ | ↑ | ↓ | ↓ | Sensorineural deafness | No | No | No | [9] |

* Abbreviations: ADH: autosomal dominant hypocalcemia; BS: Bartter syndrome; cBS: classic Bartter syndrome; DCT: distal convoluted tubule; EA1: episodic ataxia, type I; EAST syndrome: epilepsy, ataxia, sensorineural deafness, and tubulopathy syndrome; ESRD: end stage renal disease; FHHNC: familial primary hypomagnesemia with hypercalciuria and nephrocalcinosis; GS: Gitelman syndrome; HHH syndrome: hypertension, hypercholesterolemia, and hypomagnesemia syndrome; HPABH4D: hyperphenylalaninemia, BH4-deficient, type D; HSH: hypomagnesemia with secondary hypocalcemia; HSMR syndrome: hypomagnesemia, seizures, and intellectual disability syndrome; HUPRA syndrome: hyperuricemia, pulmonary hypertension, and renal failure syndrome; IDH: isolated-dominant hypomagnesemia; IRH: isolated-recessive hypomagnesemia; KCS2 syndrome: Kenny-Caffey syndrome, type 2; KICA syndrome: kidney tubulopathy and cardiomyopathy; KSS: Kearns–Sayre syndrome; NISBD2: neonatal inflammatory skin and bowel disease; PCT: proximal convoluted tubule; TALH: thick-ascending loop of Henle.

b Lesion in PCT may have characteristics of TALH and DCT tubulopathy.

c End stage renal disease.

d Deep intronic mutation.
mutations are identified in several genes responsible for inherited renal hypomagnesemia. Ramsbottom and his colleagues delivered antisense oligonucleotide (ASO)-induced splicing of the mutated exon (CEP20 G1890*) to restore protein expression in cells from a patient with Joubert syndrome [60]. Translation or protein targeting includes translational read-through, restoring proteostasis and pathway-specific therapy. Aminoglycoside and PTC124, the two main drugs of translational read-through, allow the translational machinery to bypass the premature termination code [61]. We had significantly increased survival rate and partially rescued Na’+HCO3- cotransporter 1 (NBCe1) activity ex vivo by delivering PTC124 therapy in NBCe1 p.W516* knock-in mice [62]. Cell therapy allows integrating the exogenous delivery of cells and reactivation of cellular function. The induced pluripotent stem cells from somatic cells of patients or embryonic stem cells could be used and differentiated to tubular precursor cells [63]. Of note, the genome-edited cells from patients by CRISPR-engineered cell therapies can be also used for cell therapy and has been successfully applied clinically [56,64]. The above-mentioned potential therapies required appropriate cellular and/or animal models to test the efficacy and safety in the future.

Concluding remarks

The etiologies responsible for impaired Mg²⁺ homeostasis are complex and heterogeneous, therefore, a comprehensive evaluation is essential for accurate diagnosis. After the exclusion of acquired causes, genetic causes can be further classified into defects in TALH, DCT and PCT according to the specific biochemical characteristics and extra-renal manifestations. Strategy for molecular diagnosis of inherited renal hypomagnesemia can be further stratified: patients with specific disease, disease with uncertain gene, and those with unknown gene. Algorithms for genetic testing can be developed based on the knowledge of advantages and limitations of molecular methods including direct Sanger sequencing, cDNA analysis, MLPA, gene panels, and WES. Once the causative gene is detected, prediction of clinical outcome, accurate therapeutic intervention, and genetic consulting are all facets of personalized medicine that ultimately lead to improved outcome within a shorter time frame. Although increasing numbers of genetic defects involving renal Mg²⁺ homeostasis is being identified and several molecular and cellular therapy...
is proposed, a clear understanding of underlying biomolecular mechanisms still underpins the basis of management of inherited renal hypomagnesemia.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

[1] Li FY, Chainge-Delalande B, Kanellopoulou C, Davis JC, Matthews HF, Douek DC, et al. Second messenger role for Mg2+ - revealed by human T-cell immunodeficiency. Nature 2011;475:471–6.
[2] de Baaij JHF, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. Physiol Rev 2015;95:1–46.
[3] Schimatschek HF, Remps R. Prevalence of hypomagnesemia in an unselected German population of 16,000 individuals. Magnes Res 2001;14:283–90.
[4] Cherno T, Bamberger S, Stoiko M, Vadnais M, Mills S, Hoellerich V, et al. Hypomagnesemia in patients in postoperative intensive care. Chest 1989;95:391–7.
[5] Escuela MP, Guerra M, Arazo A, et al. Total and ionized serum magnesium in critically ill patients. Intensive Care Med 2005;31:151.
[6] Yamazaki D, Funato Y, Miura J, Sato S, Toyosawa S, Furutani K, et al. Basolateral Mg2+ extrusion via CNNM4 mediates transcellular Mg2+ transport across epithelia: a mouse model. PLoS Genet 2013;9:e1003983.
[7] Le Grimmel C, Giocondi MC, Philippe P. Micropuncture study along the proximal convoluted tubule electrolyte reabsorption in first convolutions. Pflügers Arch Eur J Physiol 1975;354:133.
[8] Quamme GA, Dirks JH. The physiology of renal magnesium handling. Ren Physiol 1986;9:257.
[9] Schlingmann KP, Renigunta A, Hoorn EJ, Forst AL, Renigunta V, Atanasov V, et al. Defects in KCN16 cause a novel tubulopathy with hypokalemia, salt wasting, disturbed acid-base homeostasis, and sensorineural deafness. J Am Soc Nephrol 2021;32:1498–512.
[10] Stuiver M, Lainez S, Will C, Terryn S, Guenzel D, Debaix H, et al. Analysis of renal Mg2+ handling, is mutated in dominant inherited renal hypomagnesemia. J Clin Invest 2005;115:1651–8.
[11] Meij IC, Koenderink JB, van Bokhoven H, Assink KFH, heister K, Janssen R, et al. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. J Clin Invest 2007;117:2260–7.
[12] Meij IC, Koenderink JB, van Bokhoven H, Assink KFH, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[13] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[14] Thebault S, de Baaij JHF, van der Wijst J, van den Berg D, Janssen R, Teijpar S, et al. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. J Clin Invest 2009;119:936–42.
[15] Groenestege WMT, Thebault S, van der Wijst J, van den Berg D, Janssen R, Teijpar S, et al. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. J Clin Invest 2007;117:2260–7.
[16] Meij IC, Koenderink JB, van Bokhoven H, Assink KFH, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[17] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[18] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[19] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[20] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[21] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[22] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[23] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[24] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[25] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[26] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[27] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[28] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[29] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
[30] Schlingmann KP, Bandulik S, Hammen C, Tarailo-Graovac M, Holm R, Baumann M, et al. Germline de novo mutations in ATP1A1 cause renal hypomagnesemia, refractory seizures, and intellectual disability. Am J Hum Genet 2018;103:808–16.
Heidet L, Decramer S, Pawtowski A, Morini Lo YF, Nozu K, Iijima K, Morishita T, Huang CC, Yang S Sen, Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Guerrera MP, Volpe SL, Mao JJ. Therapeutic uses of Weglicki WB, Mak IT, Phillips TM. Blockade of cardiac Mubagwa K, Gwanyanya A, Zakharov S, Macianskiene R. Greising SM, Gransee HM, Mantilla CB, Sieck GC. Systems Gu¨ r, C¸ olpan L, Nas K, C¸ evik R, Sarac¸ J, Erdo Rodrı´guez-Mor Murakami M, Ishizuka J, Sumi S, Nickols GA, Cooper CW, Koivisto M, Valta P, H Feske S, Skolnik EY, Prakriya M. Ion channels and Mephlicki WB, Mak IT, Phillips TM. Blockade of cardiac inflammation in Mg2+ deficiency by substance P receptor inhibition. Circ Res 1994;74:1009–13. Cheng PT, Grabher JJ, LeGeros RZ. Effects of magnesium on calcium phosphate formation. Magnesium 1988;7:123–32. Munbagwa K, Gwanyanya A, Zakharov S, Macianskiene R. Regulation of calcium channels in cardiac and smooth muscle cells by intracellular magnesium. Arch Biochem Biophys 2007;458:73–89. Greising SM, Gransee HM, Mantilla CB, Sieck GC. Systems biology of skeletal muscle: ﬁber type as an organizing principle. Wiley Interdiscip Rev Syst Biol Med 2012;4:457–73. G¨ ur A, ¸Colpan L, Nas K, ¨Cevik R, Sarac¸ J, Erd¸og˘an F, et al. The role of trace minerals in the pathogenesis of postmenopausal osteoporosis and a new effect of calcitonin. J Bone Miner Metab 2002;20:39–43. Murakami M, Ishizuka J, Sumi S, Nickols GA, Cooper CW, Townsend CM, et al. Role of extracellular magnesium in insulin secretion from rat insulinoma cells. Proc Soc Exp Biol Med 1992;200:490–4. Rodrı´guez-Morãn M, Guerra-Romero F. Insulin secretion is decreased in non-diabetic individuals with hypomagnesaemia. Diabetes Metab Res Rev 2011;27:590–6. Koivist o M, Valta P, Hockerstedt K, Lindgren L. Magnesium depletion in chronic terminal liver cirrhosis. Clin Transplant 2002;16:325–8. Feske S, Skolnik EY, Prakriya M. Ion channels and transporters in lymphocyte function and immunity. Nat Rev Immunol 2012;12:532–47. Lo YF, Nozu K, Iijima K, Morishita T, Huang CC, Yang S Sen, et al. Recurrent deep intronic mutations in the SLC12A3 gene responsible for Gitelman’s syndrome. Clin J Am Soc Nephrol 2011;6:630–9. Heidet L, Decramer S, Pawtowski A, Morini Lo YF, Nozu K, Iijima K, Morishita T, Huang CC, Yang S Sen, Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1995;76:1259–65. Gao X, Peng L, Adhikari CM, Lin J, Zuo Z. Spironolactone reduced arrhythmia and maintained magnesium homeostasis in patients with congestive heart failure. J Card Fail 2007;13:170–7. Sontia B, Montezano AC, Paravicini T, Tabet F, Touyz RM. Downregulation of renal TRPM7 and increased inﬂammation and ﬁbrosis in aldosterone-infused mice: effects of magnesium. Hypertension 2008;51:915–21. Zuris JA, Thompson DB, Shu Y, Gu ¨linger JP, Bessen JL, Hu JH, et al. Cationic lipid-mediated delivery of proteins enables efﬁcient protein-based genome editing in vitro and in vivo. Nat Biotechnol 2015;33:73–80. Bennett J. Taking stock of retinal gene therapy: looking back and moving forward. Mol Ther 2017;25:1076–94. Heikkin¨a P, Tibell A, Morita T, Chen Y, Wu G, Sado Y, et al. Adenovirus-mediated transfer of type IV collagen α5 chain cDNA into swine kidney in vivo: deposition of the protein into the glomerular basement membrane. Gene Ther 2001;8:882–90. Gaj T, Gersbach CA, Barbas CF. ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. Trends Biotechnol 2013;31:39–405. Yao X, Wang X, Hu X, Liu Z, Liu J, Zhou H, et al. Homology-mediated end joining-based targeted integration using CRISPR/Cas9. Cell Res 2017;27:801–14. Daga S, Donati F, Capitani K, Croci S, Tita R, Giliberti A, et al. New frontiers to cure Alport syndrome: COL4A3 and COL4A5 gene editing in podocyte-lineage cells. Eur J Hum Genet 2020;28:480–90. Hammond SM, Wood MJ. Genetic therapies for RNA mis-splicing diseases. Trends Genet 2011;27:196–205. Tanner G, Glaus E, Barthelmes D, Ader M, Fleischhauer J, Pagani F, et al. Therapeutic strategy to rescue mutation-induced exon skipping in rhodopsin by adaptation of U1 snRNA. Hum Mutat 2009;30:255–63. Berger A, Lorain S, Josippe C, Desrosiers M, Peccate C, Vuit T, et al. Repair of rhodopsin mRNA by spliceosome-mediated RNA trans-splicing: a new approach for autosomal dominant retinitis pigmentosa. Mol Ther 2015;23:918–30. Ramsbottom SA, Molinari E, Srivastava S, Silberman F, Henry C, Alkanderi S, et al. Targeted exon skipping of a CEP290 mutation rescues Joubert syndrome phenotypes in vitro and in a murine model. Proc Natl Acad Sci U S A 2018;115:12489–94. Nagel-Wolfrum K, Moller F, Penner I, Baasov T, Wolfrum U. Targeting nonsense mutations in diseases with translational read-through-inducing drugs (TRIDs). BioDrugs 2016;30:49–74. Fang YW, Yang SS, Chau T, Nakamura M, Yamazaki O, Seki G, et al. Therapeutic effect of prenatal alkalization and PTC124 in Na+/-HCO3- - cotransporter 1 p W516* knock-in mice. Gene Ther 2015;22:374–81. Mollura DJ, Hare JM, Rabb H. Stem-cell therapy for renal failure. Am J Cardiol 2000;85:1695–702.
Van Der Made CI, Hoorn EJ, De La Faille R, Karaaslan H, Godron A, Harambat J, Boccio V, Mensire A, May A, Claverie-Martín F, Vargas-Poussou R, Müller D, García-Schlingmann KP, Konrad M, Jeck N, Waldegger P, Nozu K, Inagaki T, Fu XJ, Nozu Y, Kaito H, Kanda K, et al. Birkenh... Nozu K, Iijima K, Nozu Y, Ikegami EI, Imam T, Fu XJ, et al. A deep intrinsic mutation in the SLC12A3 gene leads to Gitelman syndrome. Pediatr Res 2009;66:590–3.

Nozu K, Nozu Y, Nakashiki M, Komoto T, Horinouchi T, Shono A, et al. Cryptic exon activation in the SLC12A3 in Gitelman syndrome. J Hum Genet 2017;62:535–7.

Chinen T, Saeki M, Mori T, Sohara E, Uchida S, Akimoto T. A case of Gitelman syndrome: our experience with a patient treated in clinical practice on a local island. J Rural Med 2019;14:258–62.

Glaudemans B, Yntema HG, San-Cristobal F, Schoots J, Pfundt R, Kamsteeg EJ, et al. Novel NCC mutants and functional analysis in a new cohort of patients with Gitelman syndrome. Eur J Hum Genet 2012;20:263–70.

De Baaij JHF, Dorresteijn EM, Hennekam EAM, Kamsteeg EJ, Meijer R, Dahan K, et al. Recurrent FXYD2 p.Gly41Arg mutation in patients with isolated dominant hypomagnesaemia. Nephrol Dial Transplant 2015;30:952–7.

Franken GAC, Müller D, Mignot C, Keren B, Lévy J, Tabet A, et al. The phenotypic and genetic spectrum of patients with heterozygous mutations in cyclin M2 (CNNM2). Hum Mutat 2021;42:473–86.

Isojima T, Doi K, Mitsui J, Oda Y, Tokuhiro E, Yasoda A, et al. A recurrent de novo FAM111A mutation causes kenny-cafeay syndrome type 2. J Bone Miner Res 2014;29:992–8.

Unger S, Görra MW, Le Bèche C, Do Vale-Pereira S, Bedeschi MF, Geilberger S, et al. FAMIL11A mutations result in hypoparathyroidism and impaired skeletal development. Am J Hum Genet 2013;92:990–5.

Paulhus K, Ammerman L, Glasscock E. Clinical spectrum of KCNA1 mutations: new insights into episodic ataxia and epilepsy comorbidity. Int J Mol Sci 2020;21:2802.

Schlingmann KP, Sassen MC, Weber S, Pechmann U, Kusch K, Peiken L, et al. Novel TRPM6 mutations in 21 families with primary hypomagnesaemia and secondary hypocalcemia. J Am Soc Nephrol 2005;16:3061–7.

Naem M, Hussain S, Akhtar N. Mutation in the tight-junction gene claudin 19 (CLDN19) and familial hypomagnesaemia, hypercalciuria, nephrocalcinosis (FHNC) and severe ocular disease. Am J Nephrol 2011;34:241–8.

Lemos M, Gonçalves JS, Correia CR, Maria AT. Neonatal inflammatory skin and bowel disease type 2: a very rare disease associated with EGFR mutation. J Pediatr Neonatal Individ Med 2021;10:1–5.

Wilson FH, Hariini A, Parhi A, Zhao H, Petersen KF, Toka HR, et al. A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. Science 2004;306:1190–4.
[99] Viering D, Schlingmann KP, Hureaux M, Nijenhuis T, Mallett A, Chan MMY, et al. Gitelman syndrome phenocopy caused by pathogenic variants in mtDNA. J Am Soc Nephrol 2022;33:305–25.

[100] Rivera H, Martín-Hernández E, Delmiro A, García-Silva MT, Quijada-Fraile P, Muley R, et al. A new mutation in the gene encoding mitochondrial seryl-tRNA synthetase as a cause of HUPRA syndrome. BMC Nephrol 2013;14:195.

[101] Sabella-Jiménez V, Otero-Herrera C, Silvera-Redondo C, Garavito-Galofre P. Mitochondrial DNA deletion and duplication in kearns–sayre syndrome (KSS) with initial presentation as pearson marrow-pancreas syndrome (PMPS): two case reports in barranquilla, Colombia. Mol Genet Genomic Med 2020;8:e1509.

[102] Katsanos KH, Elisaf M, Bairaktari E, Tsianos EV. Severe hypomagnesemia and hypoparathyroidism in Kearns-Sayre syndrome. Am J Nephrol 2001;21:150–3.

[103] Maceluch JA, Niedziela M. The clinical diagnosis and molecular genetics of kearns-sayre syndrome: a complex mitochondrial encephalomyopathy. Pediatr Endocrinol Rev 2006;4:117–37.