The genetic spectrum of Gitelman(-like) syndromes

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Purpose of review
Gitelman syndrome is a recessive salt-wasting disorder characterized by hypomagnesemia, hypokalemia, metabolic alkalosis and hypocalciuria. The majority of patients are explained by mutations and deletions in the SLC12A3 gene, encoding the Na⁺-Cl⁻-co-transporter (NCC). Recently, additional genetic causes of Gitelman-like syndromes have been identified that should be considered in genetic screening. This review aims to provide a comprehensive overview of the clinical, genetic and mechanistic aspects of Gitelman-like syndromes.

Recent findings
Disturbed Na⁺ reabsorption in the distal convoluted tubule (DCT) is associated with hypomagnesemia and hypokalemic alkalosis. In Gitelman syndrome, loss-of-function mutations in SLC12A3 cause impaired NCC-mediated Na⁺ reabsorption. In addition, patients with mutations in CLCNKB, KCNJ10, FXYD2 or HNF1B may present with a similar phenotype, as these mutations indirectly reduce NCC activity. Furthermore, genetic investigations of patients with Na⁺-wasting tubulopathy have resulted in the identification of pathogenic variants in MT-TI, MT-TF, KCNJ16 and ATP1A1. These novel findings highlight the importance of cell metabolism and basolateral membrane potential for Na⁺ reabsorption in the DCT.

Summary
Altogether, these findings extend the genetic spectrum of Gitelman-like electrolyte alterations. Genetic testing of patients with hypomagnesemia and hypokalemia should cover a panel of genes involved in Gitelman-like syndromes, including the mitochondrial genome.

Keywords
Gitelman syndrome, mitochondria, Na⁺-Cl⁻-co-transporter, salt-wasting, tubulopathy

INTRODUCTION

Gitelman syndrome is a recessive salt-wasting disorder characterized by hypomagnesemia, hypokalemia, metabolic alkalosis, hypocalciuria and activation of the renin-angiotensin-aldosterone system (RAAS) [1,2]. Patients often present in late childhood or early adulthood with nonspecific symptoms, including muscle weakness, tetany, hypotension and fatigue [3,4]. Typical complaints may also include salt craving and thirst as a reflection of salt-wasting. Gitelman syndrome is not a benign condition and may cause chondrocalcinosis due to hypomagnesemia, prolonged QTc interval and arrhythmias due to hypokalemia, glucose intolerance and immunodeficiencies [5–8]. The disease was first described in 1966 by Hillel Gitelman as a subtype of Bartter syndrome [2]. However, typical Bartter symptoms such as polyhydramnios, hypercalciuria, nephrocalcinosis, failure to thrive and an antenatal presentation are rare in Gitelman syndrome. Indeed, genetic investigations in the 1990s revealed that Bartter and Gitelman syndrome are separate clinical entities [9–13].

Classic Gitelman syndrome is caused by biallelic mutations in solute carrier 12 subtype 3 (SLC12A3) encoding the Na⁺-Cl⁻-co-transporter (NCC), which is exclusively expressed in the distal convoluted tubule (DCT) [13]. The NCC facilitates apical Na⁺ and Cl⁻ transport in the DCT and is the therapeutic target of thiazide diuretics. As a consequence of impaired NCC-mediated Na⁺ reabsorption in the DCT, the Na⁺ delivery to the collecting duct is increased. Accompanied by RAAS activation, the high Na⁺ delivery results in increased K⁺ secretion in the collecting duct explaining the hypokalemia in
## KEY POINTS

- Gitelman syndrome is a Na\(^{+}\)-wasting tubulopathy explained by reduced activity of the Na\(^{+}\)-Cl\(^{-}\) co-transporter (NCC) in the distal convoluted tubule.
- Patients with pathogenic variants in \(\text{SLC12A3}, \text{MT-TI}, \text{MT-TF}, \text{CLKNB}, \text{KCNJ10}, \text{KCNJ16}, \text{ATP1A1}, \text{FXYD2}\), and \(\text{HNF1B}\) may present with a Gitelman-like phenotype.
- Genetic testing of patients with suspected Gitelman syndrome should extend beyond \(\text{SLC12A3}\) and should also include the mitochondrial genome.

Gitelman patients. The metabolic alkalosis develops secondary to hypokalemia. The hypomagnesemia is less well understood (extensively reviewed in [14]), but it is generally thought that a reduced DCT mass is a major contributor to this defect [15]. However, human data supporting this hypothesis are scarce.

In recent years, several seminal discoveries have been made to resolve the missing heritability in Gitelman syndrome [16,17**]. This review, therefore, provides an overview of all known genetic causes of Gitelman-like syndromes. The differences in clinical presentation, genetic inheritance and molecular disease mechanism will be discussed.

### SLC12A3 – CLASSIC GITELMAN

In 1996, Simon et al. [2] described homozygous and compound heterozygous loss-of-function mutations in \(\text{SLC12A3}\) as cause of Gitelman syndrome. Since then, 133 pathogenic variants have been described (ClinVar, February 2022), including deletions, splice site variants and intronic variants. In most recent screenings, approximately 75% of patients with a Gitelman syndrome presentation are diagnosed with a biallelic mutation in \(\text{SLC12A3}\) [18,19]. Of them, 20–25% have a homozygous pathogenic variant, 60–70% are compound heterozygous and ±10% have genomic rearrangements (deletion/duplication), which can be picked up by multiplex ligation-dependent probe amplification (MLPA) [18].

Homozygous mutations have been associated with an earlier age of onset and more severe hypocalciuria in a Chinese cohort [19]. In contrast, no phenotypic differences were reported for genomic rearrangements.

In-depth phenotyping of Gitelman patients with \(\text{SLC12A3}\) mutations has resulted in the identification of subclinical phenotypes [5,20*]. In a large European cohort, 20% of patients with Gitelman syndrome had hypoparathyroidism [20*]. As the parathyroid hormone (PTH) and magnesium concentrations were correlated in this cohort, it has been hypothesized that the hypoparathyroidism is explained by Mg\(^{2+}\)-dependent regulation of the calcium-sensing receptor [21]. Alternatively, a positive Ca\(^{2+}\) balance may contribute to hypoparathyroidism in Gitelman syndrome. Several studies reported increased fasting glucose levels and insulin resistance in Gitelman patients [5,22,23]. In a large cohort of 77 patients, the insulin response was almost doubled upon glucose loading, which was associated with a significant increase of the insulin resistance index [5]. Indeed, diabetes mellitus has been reported in one-third of the patients in a Chinese cohort study [24]. Again, hypomagnesemia may (partially) explain the insulin resistance in Gitelman syndrome, as Mg\(^{2+}\) is essential for the insulin signalling pathway [25,26].

Interestingly, only one pathogenic variant is discovered in 10–15% of all Gitelman patients, even after screening for genomic rearrangements [18]. In these cases, mutations may be present in regulatory regions such as promoters and introns. Moreover, two patients were reported with a digenic inheritance pattern consisting of a heterozygous \(\text{SLC12A3}\) variant and a heterozygous \(\text{CLKNB}\) variant [27,28]. However, it should be noted that it has not been conclusively demonstrated that digenic inheritance can cause Gitelman syndrome. Given that 2–8% of the population are carriers of one pathogenic \(\text{SLC12A3}\) variant and the percentage of carriers of one pathogenic \(\text{CLKNB}\) variant may be similar, many patients should be affected by such an inheritance pattern [29].

Carriers of a single heterozygous pathogenic variant in \(\text{SLC12A3}\) were longtime considered healthy. However, recent studies have demonstrated the presence of a subclinical phenotype in heterozygous carriers [5,30**]. Plasma aldosterone was slightly increased in carriers of heterozygous pathogenic \(\text{SLC12A3}\) variants [5]. Moreover, heterozygous carriers exhibited a slightly higher plasma Ca\(^{2+}\) concentration and lower plasma PTH concentration compared with controls. A recent study in the Old Order Amish population demonstrated that heterozygous carriers of the pathogenic p.R642G variant had significantly lower serum potassium levels than noncarriers [30**]. These clinical findings are in line with mechanistic studies demonstrating the close connection of NCC and K\(^{+}\) regulation, termed the ‘potassium switch’ [31]. In short, the potassium switch turns on NCC in response to low dietary K\(^{+}\) intake and off in response to high K\(^{+}\) intake (Fig. 1) [32,33]. As such, K\(^{+}\) is currently considered as the main regulator of NCC activity, acting as a natural thiazide diuretic [34].

Altogether, these studies demonstrate that common genetic variants and heterozygous pathogenic
variants in \textit{SLC12A3} may contribute to subclinical phenotypes in the general population.

\textbf{MT-TI / MT-TF – MITOCHONDRIAL GITELMAN}

In 2004, Lifton \textit{et al.} [35] first described mutations in the mitochondrial transfer RNA (tRNA) for isoleucine, encoded by the \textit{MT-TI} gene, in a large family with renal hypomagnesemia, hypokalemia and hypocaliuria. Only recently, these findings were confirmed in 10 additional families with a maternal inheritance pattern [17**]. A large European collaboration demonstrated that mitochondrial DNA variants in \textit{MT-TI} and \textit{MT-TF} are causative for a Gitelman-like syndrome [17**]. Interestingly, the \textit{MT-TF} mutations were also associated with chronic kidney disease, whereas patients with \textit{MT-TI} mutations showed a preserved kidney function [17**]. Hypertension and dyslipidemia that were originally described to be part of the phenotype were not reported in these additional families, questioning whether this initial association was correct.

The identification of mitochondrial DNA mutations demonstrated the essential role of mitochondria for renal Na\(^+\) reabsorption. The DCT cell is the most mitochondria-rich cell type within the kidney in order to meet the high energy demand required for electrolyte transport [36]. In patient fibroblasts, the identified \textit{MT-TI} and \textit{MT-TF} mutations were demonstrated to reduce mitochondrial function [17**]. Although the exact mechanisms remain unclear, pharmacological inhibition of complex IV, mimicking the effect of the mtDNA variants, inhibited NCC phosphorylation and NCC-mediated Na\(^+\) uptake [17**]. However, it should be noted that only specific \textit{MT-TI} and \textit{MT-TF} mutations are associated with a Gitelman-like phenotype. Particularly, the m.591C>T and m.4291T>C variants are hotspot mutations. Other \textit{MT-TI} and \textit{MT-TF} mutations also resulting in reduced mitochondrial function have been associated with other syndromes such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged-red fibres (MERRF) [37]. Consequently, one may consider additional pathophysiological mechanisms such as disturbances in tRNA modifications or effects of mitochondrial DNA fragments [38,39].

\textbf{CLCNKB – BARTTER TYPE 3}

Although recessive \textit{CLCNKB} mutations have originally been described to cause classic Bartter syndrome (type 3), a systematic analysis of a large cohort of patients demonstrates that 25% of all patients present with a Gitelman syndrome phenotype [10,40,41]. In fact, some patients may initially
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show symptoms of Bartter syndrome and develop a
typical Gitelman phenotype in later childhood or
adolescence [42]. Consequently, genetic screening
of patients with a clinical diagnosis of Gitelman
syndrome quite regularly turn out to have CLCKNB
mutations upon genetic screening [43,44]. As large
deletions account for up to 40% of all cases of
Bartter syndrome type 3, testing for structural
variations by MLPA or other means is advised
[41]. Compared with classic Gitelman syndrome,
patients with CLCKNB mutations have generally an
earlier age of initial presentations and slightly
higher serum Mg2⁺ and urinary Ca²⁺ concentrations
[45,46]. Patients with CLCKNB mutations may
additionally develop chronic kidney disease
(up to 25%), nephrocalcinosis (10–20%) or growth
retardation [41,46].

CLCKNB encodes the CLCkb Cl⁻ channel that is
expressed in the TAL, DCT and collecting duct. Loss-
of-function mutations in CLCkb result in an
increased intracellular Cl⁻ concentration. As Cl⁻
inhibits WNK kinases, an increased Cl⁻ concentration
causes reduced NCC activity by inhibition of the
WNK-SPAK/OSR1 pathway (Fig. 1) [34,47,48]. A
similar regulatory mechanism of NKCC2 exists in
the TAL, which explains why CLCkb mutations may
result in both Bartter-like and Gitelman-like syn-
dromes [49]. In general, hypochloremia and
increased fractional excretions of Na⁺ and Cl⁻ are
more severe in Bartter syndrome type 3 than in
Gitelman syndrome, which may reflect that both
TAL and DCT are affected by CLCKNB mutations
[45].

KCNJ10/ KCNJ16 – EAST / SESAME

The acronym EAST/SeSAME syndrome describes a
disease entity with autosomal recessive inheritance
combining epilepsy, ataxia, sensorineural deafness
and renal tubulopathy with/without mental retardation
[50,51]. Patients usually present early in
infancy with seizures, developmental delay and
ataxia. The renal phenotype closely resembles Gitel-
man syndrome comprising hypokalemic alkalosis,
hypomagnesemia and hypocalciuria. EAST/SeSAME
syndrome is caused by loss-of-function mutations in
the KCNJ10 gene encoding the inwardly rectifying
K⁺-channel Kir4.1 [50,51]. In the kidney, Kir4.1 is
predominantly expressed at the basolateral mem-
brane of cTAL, DCT and CNT cells. Here, it forms
eheteromers with its close homologue Kir5.1
(KCNJ16). Kir4.1/Kir5.1 potassium channels serve
as a K⁺ sensor of DCT cells [14,34] that allow for a
recycling of K⁺ to drive Na⁺-K⁺-ATPase activity
[32,52]. Uncoupling of this ‘pump-leak mecha-
nisms’ will result in depolarization of the basolateral
membrane and increased intracellular Cl⁻ concen-
trations, similar to mutations in CLCkb (Fig. 1) [10].
Consequently, the WNK-SPAK/OSR1 signalling
cascade is inhibited resulting in reduced NCC activity.

Recently, recessive loss-of-function mutations
have also been described in KCNJ16 leading to a
tubulopathy with deafness [16*,53]. Apart from
renal salt wasting and hypokalemia, patients may
present with opposite changes in acid-base metab-
olism that are thought to result from a broader
expression pattern and more diverse tasks of
Kir5.1: In addition to its role in the DCT outlined
above, Kir5.1 also forms heteromers with Kir4.2
(KCNJ15) in the proximal tubule that are critical
for bicarbonate reabsorption and ammonia excre-
tion [54]. However, if distal tubular salt wasting
predominates, patients with KCNJ16 mutations
may present with hypokalemic alkalosis and a Gitel-
man syndrome-like phenotype [16*].

ATP1A1/ FXYD2 – Na⁺-K⁺-ATPase
dysfunction

More than two decades ago, a missense mutation in
FXYD2 encoding the γ-subunit of Na⁺K⁺-ATPase
was described in two related families. The index
patients presented with seizures during childhood
and profound hypomagnesemia [55,56]. Laboratory
investigations revealed low serum Mg²⁺ levels also
in numerous, apparently healthy family members.
In addition, urinary Ca²⁺ excretion rates were found
to be low, a finding reminiscent of patients present-
ing with Gitelman Syndrome. Later, a careful bio-
chemical workup in members of two additional
families with the identical mutation also revealed a
tendency towards hypokalemia and metabolic
alkalosis. Additional clinical findings in affected
members of these families comprised muscle cramps,
seizures and chondrocalcinosis [55–57].

Members of the FXYD protein family constitute
a third, tissue-specific γ-subunit of Na⁺K⁺-ATPase.
FXYD2 is expressed in the distal nephron, especially
in the DCT and connecting tubule [58]. Here, the
FXYD2 γ-subunit increases the apparent affinity
of Na⁺-K⁺-ATPase for ATP while decreasing its Na⁺
affinity providing a mechanism for balancing
energy utilization and maintaining appropriate salt
gradients [59]. Expression studies of mutant p.G41R-
FXYD2 revealed a dominant-negative effect lead-
ting to a retention of the γ-subunit in the Golgi complex
[60].

Recently, also heterozygous de-novo mutations
in the α1-subunit of Na⁺K⁺-ATPase (ATP1A1) have
been described leading to severe hypomagnesemia
due to renal magnesium wasting [61]. Affected chil-
dren presented in infancy with seizures that were
Hypomagnesemia and hypocalciuria are common in patients with heterozygous HNF1β mutations and deletions [63–66]. In a minor group of patients, these electrolyte disturbances are accompanied by hypokalemia and metabolic alkalosis [67,68] (Table 1). In addition, patients with HNF1β nephropathy often present with symptoms beyond a Gitelman-like phenotype including, but not limited to, tubule interstitial kidney disease (ADTKD), renal cysts, renal hypoplasia, hyperuricemia, hyperparathyroidism, maturity-onset diabetes of the young (MODY5), neurodevelopmental disorders, or genital anomalies [64–72]. Approximately 50% of ADTKD-HNF1β patients develop chronic kidney disease [67,71,73]. HNF1β defects are therefore among the most common causes of childhood kidney transplantation [74,75]. Interestingly, in some cases, the electrolyte disturbances might represent the first symptom of the disease [63]. Consequently, the initial diagnosis of HNF1β nephropathy has sometimes been Gitelman syndrome, until genetic investigations revealed mutations in the HNF1β gene [43]. Of note, renin-angiotensi-n-aldosterone system (RAAS) activation is scarce in patients with HNF1β defects, whereas it is one of the main symptoms of Gitelman syndrome. Moreover, hypertension is present in 22% of children with HNF1β nephropathy [76]. Gitelman patients are generally hypertensive compared with healthy family members, though cases with hypertension in later life have been described [6,77]. Several reports noted that young children with HNF1β defects have

HNF1B – ADTKD-HNF1B

Hypomagnesemia and hypocalciuria are common in patients with heterozygous HNF1β mutations

Table 1. Overview of Gitelman-(like) syndromes

| Gene | Protein | Disease | OMIM | Inh. | Onset | Mg²⁺ | K⁺ | HCO₃⁻ | FECA²⁺ | RAAS | Other symptoms | Ref |
|------|---------|---------|------|------|-------|-------|-----|-------|--------|------|----------------|-----|
| SLC12A3 | NCC | Classic Gitelman syndrome | 263800 | R | Childhood | adolescence | ↓ | ↓ | ↑ | ↓ | ↑ | Chondrocalcinosis | [1,2,13,46] |
| MT1I | Mitochondrial tRNAlle | Mitochondrial Gitelman syndrome | M | Adult | ↓ | ↓ | →/↓ | ↓ | ←/↓ | CKD | [17**,35] |
| MT1F | Mitochondrial tRNAPhe | Mitochondrial Gitelman syndrome | M | Childhood | Adult | ↓ | ↓ | →/↓ | ↓ | ←/↓ | CKD | [17**] |
| CLCNKB | CIc₆,₇ | Bartter syndrome type III | 607364 | R | Neonatal | Childhood | ↓ | ↓ | ↑ | ↓ | ↑ | CKD | [10,45,46] |
| KCNJ10 | Kir4.1 | SESAME / EAST syndrome | 612780 | R | Neonatal | ↓ | ↓ | ↑ | ↓ | ↑ | Epilepsy, ataxia, sensorineural deafness | [50,51] |
| KCNJ16 | Kir5.1 | | 619406 | R | ↓ | ↓ | ↓ | ↓ | ↓ | ↑ | Deafness | [16*,53] |
| FXYD2 | γ-subunit of the Na⁺-K⁺-ATPase | 154020 | D | Childhood | Adult | ↓ | ←/→ | ↓ | Chondrocalcinosis | [56,57] |
| ATP1A1 | α-subunit of the Na⁺-K⁺-ATPase | 618314 | D | Neonatal | ↓ | ↓ | → | ← | ← | Intellectual disability | [61] |
| HNF1B | HNF1β | ADTKD-HNF1B | 137920 | D | Neonatal | Childhood | ↓ | ↓ | ↑ | ↓ | →/← | CKAUT MODYS | [66,68] |
generally higher serum Mg\(^{2+}\) levels than older patients [63,68,72]. It has, therefore, been proposed that hypomagnesemia developed later in childhood. However, Kolbuc et al. [65] recently showed that serum Mg\(^{2+}\) levels are also higher in early childhood of healthy controls. Consequently, the reference range of 0.7–1.1 mmol/l may not be suitable for young children, resulting in an underestimation of healthy controls. Consequently, the reference regulatory pathway towards NCC, including regulating the expression of several proteins in the response to thiazide [80]. In line with these findings, NCC expression is decreased in kidney-specific knock-out mice [79].

In the DCT, HNF1\(\beta\) acts a transcription factor that regulates the expression of several proteins in the regulatory pathway towards NCC, including FXYD2 and KCNJ16 [69,78,79]. Potassium channel Kir4.1/Kir5.1 and the Na\(^+-K\(^{+}\)-ATPase activity are both essential components of the ‘pump-leak mechanism’ regulating the membrane potential and basolateral Cl\(^{-}\) transport. Disturbed transcription of FXYD2 and KCNJ16 thereby results in reduced NCC activity by the same mechanisms as described above. Clinical studies confirmed that ADTKD-HNF1\(\beta\) patients have reduced NCC activity, as indicated by a diminished response to thiazide [80]. In line with these findings, NCC expression is decreased in kidney-specific HNF1\(\beta\) knock-out mice [79].

OTHER GENES
Several other non-Bartter, non-Gitelman syndromes are associated with salt-wasting, hypomagnesemia and hypokalemic alkalosis. Although these syndromes are independent of NCC dysfunction and therefore do not present as classical Gitelman syndrome, the presentation of individual patient may sometimes be, at least partially, similar.

Hypomagnesemia, hypokalemia and metabolic alkalosis are the cardinal symptoms of patients with mTOR-activating mutations in RRAGD, encoding a small Rag GTPase [81]. These patients often present with nephrocalcinosis and/or cardiomyopathy. As this disorder is often associated with renal Ca\(^{2+}\) wasting, it is hypothesized that RRAGD mutations primarily cause a defect in the TAL [81]. However, DCT defects cannot be excluded as RRAGD is also expressed in this segment of the nephron [81].

Impaired transcellular transport in the TAL is also the cause of salt-wasting in patient with CLDN10 mutations. Patients suffer from hypokalemic hypochloremic alkalosis and RAAS activation, but generally present with hypermagnesemia [82,83]. Additional symptoms of CLDN10 patients include dysfunctional salivary, sweat and lacrimal glands [83].

Hypomagnesemia is frequently associated with hypokalemia. This effect is generally explained by the inhibitory effect of Mg\(^{2+}\) on ROMK-mediated K\(^{+}\) secretion in the distal nephron [84]. In case of Mg\(^{2+}\) deficiency, more K\(^{+}\) is wasted in the urine resulting in hypokalemia. Genetic syndromes of isolated hypomagnesemia, for example by mutations in TRPM6, KCNA1, EGF, CNNM2 or PCBD1 may therefore present with transient episodes of hypokalemia [85–91]. However, these patients are generally without metabolic alkalosis or RAAS activation.

NONGENETIC CAUSES OF Gritelman-Like Electrolyte Abnormalities
Although it goes beyond the scope of this review to discuss all noninherited conditions that can mimic the presentation of Gitelman syndrome, it is important to consider alternative causes of Gitelman syndrome in clinical practice. In particular, abuse of diuretics (most notably thiazides) may result in an identical presentation [92,93]. In addition, chronic use of proton-pump inhibitors, aminoglycosides or laxatives is accompanied by hypokalemia and hypomagnesemia, although metabolic alkalosis is generally absent [92]. Other causes of hypokalemia may include chronic vomiting and primary hyperaldosteronism, but the latter condition is associated with hypertension and a suppressed RAAS [94]. Further guidance on the clinical workup and treatment of Gitelman syndrome is provided by KDIGO [1].

CONCLUSION AND PERSPECTIVES
The discovery of SLC12A3 mutations in the 1990s established a defective salt reabsorption in the DCT as the underlying pathophysiology of Gitelman syndrome. Genetic heterogeneity of Gitelman syndrome was first demonstrated by the discovery of CLCNKB mutations in patients with a typical Gitelman syndrome-like phenotype. Since then, advances in genetics have led to the discovery of a growing number of hereditary disorders that present with the pathognomonic Gitelman syndrome signature comprising hypokalemic alkalosis, hypomagnesemia and hypercalciuria. Beyond representing important differential diagnoses for the molecular screening of affected patients, these entities not only underline the complex integrative role, but also vulnerability of the Na\(^{+}\) reabsorption machinery in the DCT. Here, transport processes are particularly dependent on cellular electrolyte homeostasis, energy level, respiratory capacity and regulatory pathways. This hereditary and phenotypic complexity will have to be taken into account by NGS-based analytic techniques as well as genetic counselling of the affected families. It appears reasonable to assume that future genetic studies will further expand the spectrum of disorders leading to defective DCT-mediated salt reabsorption or exhibiting the Gitelman syndrome-triad of hypokalemic
alakosis, hypomagnesemia and hypocalciuria as part of a more complex phenotype.

Acknowledgements

None.

Financial support and sponsorship

This work was financially supported by ZonMW under the frame of EJPRD, the European Joint Programme on Rare Diseases (EJPRD2019–40) and by the IMAGEN project, which is co-funded by the PPP Allowance made available by Health–Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships (Implementation of Advancements in GENetic Kidney Disease, LSHM20009) and the Dutch Kidney Foundation (No. 101040682). In addition, this project has received funding from the European Union’s Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP No. 825575 and the European Research Council (IN-2012-308508) and the Dutch Kidney Foundation (No. 101040682).

Conflicts of interest

There are no conflicts of interest.

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* of special interest
** of outstanding interest

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