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Review

Monogenic features of urolithiasis: A comprehensive review

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Abstract *Objective:* Urolithiasis formation has been attributed to environmental and dietary factors. However, evidence is accumulating that genetic background can contribute to urolithiasis formation. Advancements in the identification of monogenic causes using high-throughput sequencing technologies have shown that urolithiasis has a strong heritable component.
Methods: This review describes monogenic factors implicated in a genetic predisposition to urolithiasis. Peer-reviewed journals were evaluated by a PubMed search until July 2023 to summarize disorders associated with monogenic traits, and discuss clinical implications of identification of patients genetically susceptible to urolithiasis formation.
Results: Given that more than 80% of urolithiases cases are associated with calcium accumulation, studies have focused mainly on monogenetic contributors to hypercalciuric urolithiases, leading to the identification of receptors, channels, and transporters involved in the regulation of calcium renal tubular reabsorption. Nevertheless, available candidate genes and linkage methods have a low resolution for evaluation of the effects of genetic components versus those of environmental, dietary, and hormonal factors, and genotypes remain undetermined in the majority of urolithiasis formers.
Conclusion: The pathophysiology underlying urolithiasis formation is complex and multifactorial, but evidence strongly suggests the existence of numerous monogenic causes of urolithiasis in humans.

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1. Introduction

The incidence of urolithiasis has been estimated to be 11% in males and 7% in females among the general population [1]. However, the incidence of urolithiasis in individuals with a family history of urolithiasis has been shown to be three-fold higher than in patients without a family history, suggesting that urolithiasis and its factors have a strong genetic predisposition [2,3]. Investigations have reported a familial history of urolithiasis in up to 37% of patients while the proportion is 4%—12% in the healthy cohort, suggesting a heritability of urolithiasis between 0.46 and 0.63 [4,5]. More recently, improvements in high-throughput sequencing technologies capable of sequencing multiple DNA molecules in parallel have detected causative mutations in 46.7% (14/30) of analyzed genes, with 11.4% of adult cases and 20.8% of pediatric cases identified as having a monogenic cause [6]. Moreover, genome-wide association and candidate gene studies regarding the contribution of polygenic influences from multiple loci have reported that multiple genes and molecular pathways contribute to stone formation. Overall, the pathophysiology of stone formation is currently accepted to have a complex etiology that can involve a monogenic disorder or polygenic traits, dietary and hormonal components, and environmental factors [7—10].

In this review, it is our hope that improved diagnoses and better pathophysiological understanding of these disorders will lead to novel personalized diagnostic, therapeutic, and prophylactic approaches for future recurrent urolithiasis formers.

2. Heritable features of urolithiasis

2.1. Non-urinary factors

The exact role of non-urinary factors associated with a genetic predisposition to urolithiasis is not entirely clear. To date, studies on heritability have mainly focused on abnormal calcium metabolism involving serum calcium and 1,25$(OH)_2$ vitamin D. Investigations of the heritability of urolithiasis regarding non-urinary factors have focused on metabolic syndrome, with stone formation being considered a comorbid risk factor [11]. However, the underlying mechanisms linking urolithiasis risk and metabolic syndrome are unclear and are probably related to non-genetic common features associated with the two conditions.

2.2. Urinary factors

2.2.1. Calcium excretion

Evidence on the heritability of urinary traits is the strongest for excessive urinary calcium excretion, observed in up to 40% of adult patients with family history and in up to 10% of such pediatric patients [12]. Hypercalciuria can occur in isolation or in relation to metabolic disorders and can result from excessive intestinal absorption, impaired renal reabsorption, and/or excessive skeletal mobilization [13,14]. It is difficult to define the normal range of urine calcium excretion as this depends on patient age and dietary patterns; however, excess urine calcium excretion is widely defined as a 24 h excretion higher than 4 mg/kg or 0.1 mmol/kg [15].

Overall, the available evidence indicates that urinary calcium excretion has a strong heritable component. In terms of heritability, which reflects how much variation is due to underlying genetic factors, the heritability of primary hypercalciuria was initially reported by Coe et al. [16] to be 43% among first-degree relatives and 36% among all relatives. In a family-based study of metabolic phenotypes, metabolic risk factors and phenotypes were evaluated and compared in families with at least two siblings with a previous history of calcium-component urolithiasis [17]. Herein, urine calcium excretion was the only phenotype related to calcium-component urolithiasis. Moreover, daily urine calcium excretion was elevated in affected siblings relative to unaffected siblings, suggesting that hypercalciuria could be a hereditary trait. The Genetic Epidemiology Network of Arteriopathy (GENOA) cohort data were analyzed to further investigate the heritability of urinary calcium excretion [18]. Supersaturation was measured in 811 members of families in Rochester, MN, USA. Based on 24 h urine samples, urine calcium excretion showed strong heritability, along with magnesium and citrate excretion. In addition, in a study involving 12 sets of healthy homozygous twins, excretion of urine calcium showed a heritability factor of 0.94 [19]. Overall, the available evidence indicates that urine calcium excretion is a heritable feature of urolithiasis formation.

2.2.2. Citrate excretion

Hypocitraturia plays an important role in the formation of kidney stones and is present in approximately 60% of patients who develop calcium oxalate urolithiasis [20]. Hypocitraturia is usually associated with distal renal tubular acidosis (dRTA) with decreased renal citrate excretion. Low vegetable and fruit intake, and high animal protein intake can also contribute to hypocitraturia [21]. Results from the GENOA cohort showed significant heritability of urine citrate excretion, with an estimated heritability of 0.36 [18]. In a healthy homozygous twin study, urine citrate excretion had a heritability of 0.95 [19].

2.2.3. Other factors

Urine oxalate and uric acid excretion also were heritable in the healthy homozygous twin study, whereas urine magnesium excretion was heritable in the GENOA cohort [19,22,23]. The GENOA cohort was used to systematically estimate heritability and genetic correlation of numerous urinary traits associated with the risk of kidney stones using variance component methods [18]. Herein, low urine volume, a well-established risk factor for urolithiasis formation and recurrence, was observed to be significantly heritable, implicating genetic regulation of thirst. The proposed mechanisms underlying these observations were genetic regulation of pathways that affect thirst, the release of vasopressins, and vasopressin receptors in the collecting duct [24].

2.3. Dietary factors

Numerous dietary components including oxalate, calcium, sodium, protein, and fluid consumption are strongly associated with the risk of urolithiasis formation as they influence the excretion of urinary lithogenic components [22,25]. Although diet is considered an environmental factor, increasing evidence suggests dietary preferences to be partially hereditary [22,26]. The heritability of dietary traits was explored in the Erasmus Rucphen Family Study, which included 1690 individuals and utilized self-report questionnaires to evaluate the duration in which each individual consumed vegetables, fruit, fruit juice, fish, unhealthy snacks, fast food, and soft drinks; principal component analysis showed a heritability of up to 0.32 for dietary traits, suggesting that specific dietary intake patterns are heritable [25]. Dietary traits were also shown to be associated with urolithiasis in the GENOA cohort, in which dietary intake is assessed using the Viocare Food Frequency Questionnaire; animal and dietary proteins, oxalate, calcium, fructose, and sucrose consumption are identified as relevant factors [18]. These study findings suggest the presence of a genetic predisposition for dietary and eating behaviors that increase the risk of urolithiasis in certain patients.

3. Monogenic disorders

Monogenic contributions to urolithiasis formation have been considered rare. However, improvements in high-throughput sequencing technologies have helped to identify new genetic causes of urolithiasis, and suggest that a considerable proportion of all causes of urolithiasis have these traits (Table 1). One prospective study revealed that a single-gene mutation accounted for 11.4% of adult and 20.8% of pediatric urolithiasis cases [27]. The prevalence of monogenic genes was explored by high-throughput exon sequencing in an international pediatric renal stone cohort of 143 patients. Likely causative mutations were detected in 46.7% (14/30) of analyzed genes, with a molecular diagnosis in 16.8% (24/143) of patients [28]. In a whole-exome sequencing study involving 51 families who presented with a least one kidney stone before the age of 25 years, a monogenic causative mutation was noted in 29.4% (15/51) of families [29]. In this study, younger age at the diagnosis of urolithiasis, presence of multiple affected family members, and consanguinity were factors associated with higher rates of monogenic mutations.

3.1. Disorders associated with calcium-component urolithiasis

More than 80% of urolithiases are associated with calcium components, and the majority of investigations into monogenic causes of urolithiases have focused mainly on disorders related to calcium component urolithiasis. Hypercalciuria is the most commonly observed metabolic abnormality in patients with urolithiasis [30—33].

3.1.1. Autosomal dominant hypocalcemia (ADH) with hypercalciuria

ADH is attributed to heterozygous gain-of-function mutations within the calcium-sensing receptor (CaSR) signaling pathway. To date, more than 40 mutations associated with CaSR have been reported in patients with ADH, and over 50% of these were identified in the extracellular domain [34,35]. ADH type 1 is featured by mutations in the G protein-coupled protein CaSR, whereas ADH type 2 is characterized by mutations in the G protein subunit signaling partner Gα11, encoded by *GNA11*. The molecular aberrations involved in ADH are unidentified in approximately 30% of patients [36].

Patients with ADH have hypocalcemia, hyperphosphatemia, and hypomagnesemia. Most of the patients are asymptomatic; however, neurological symptoms such as carpopedal spasms or seizures have been reported [37]. The level of serum phosphate is increased or within the upper normal range and the level of serum magnesium is low or within the lower normal range in patients with hypoparathyroidism and pseudo-hypoparathyroidism [37]. However, patients with ADH with hypercalciuria have low to normal range of serum parathyroid hormone and are not hypoparathyroid or pseudo-hypoparathyroid [38].

Hypercalciuria is observed in approximately one-tenth of patients, predisposing these patients to urolithiasis. Therefore, administration of active vitamin D metabolites with the goal of adjusting for hypocalcemia can provoke hypercalciuria and subsequent risk of urolithiasis formation. Although cessation of vitamin D administration has shown to be partially reversible, it should be avoided in patients and family members with ADH whose hypocalcemia is due to a gain-of-function CaSR mutation [37].

3.1.2. Bartter syndrome

Bartter syndrome is an autosomal recessive renal tubulopathy associated with a defect in sodium chloride reabsorption in the loop of Henle. This results in extracellular fluid volume depletion with low to normal blood pressure [35]. Bartter syndrome comprises numerous electrolyte imbalances such as low potassium and chloride. The acid-base manifestation is metabolic alkalosis, with high renin, secondary hyperaldosteronism, and an increased level of prostaglandin E2 [39]. Hypercalciuria is usually evident, whereas nephrocalcinosis is mostly noted in Bartter syndromes I, II, and V [40]. Mutations in six genes are associated with Bartter syndrome.

Bartter syndrome type I is related to mutations in the gene that encodes the bumetanide-sensitive $Na^+—K^+—2Cl^-$ symporter (*NKCC2*). Bartter syndrome type II is exerted by a mutation in the ATP-sensitive inward rectifier potassium channel 1 (*ROMK*). Bartter syndrome types I and II are frequently associated with nephrocalcinosis during the antenatal or postnatal period [40]. Bartter syndrome type II is characterized by hyperkalemia in infancy and hypokalemia in the postnatal period [41]. While the optimal management of metabolic imbalances observed in this disorder is unclear, the COX inhibitor indomethacin has shown efficacy in pediatric Bartter syndrome, while K-sparing diuretics or angiotensin-converting enzyme

Table 1 Monogenic disorders of urolithiasis.

Disorder	Gene	Inheritance	Phenotype
Autosomal dominant idiopathic hypercalciuria	• *ADCY10* and *VDR*	AD	• Normocalcemia and normal PTH
Autosomal dominant hypocalcemia with hypercalciuria	• *CASR* and *GNA11*	AD	• Hypocalcemia, hyperphosphatemia, hypomagnesemia, and low to normal range PTH
Bartter syndrome			
Type I	• *NKCC2* (*SLC12A1*)	AR	• Antenatal or postnatal nephrocalcinosis, hypokalemia, and metabolic alkalosis
Type II	• *ROMK* (*KCNJ1*)	AR	• Antenatal/postnatal nephrocalcinosis, hyperkalemia in infancy, postnatal hypokalemia, late-onset nephrocalcinosis, and CKD
Type III	• *CLCNKB*	AR	• Hypokalemic metabolic alkalosis, neph rocalcinosis, and late-onset symptoms
Type IVa	• *BSND*	AR	• Sensorineural hearing loss and early-onset CKD
Type IVb	• *CLCNKB* and *CLCNKA*	AR	• Renal salt wasting and sensorineural hearing loss
Type V	• *MAGED2*	XLR	• Salt wasting, polyuria, hypokalemia, nephrocalcinosis, and antenatal onset
Dent disease			
Type 1	• *CLCN5*	XLR	• LMW proteinuria, nephrocalcinosis, and CKD with progression to ESRD
Type 2	• *OCRL*	XLR	• LMW proteinuria and nephrocalcinosis (less frequent than type 1)
Hereditary hypophosphatemic rickets with hypercalciuria	• *SLC34A1*, *SLC34A3*, and *SLC9A3R1*	AR	• Low serum phosphate, hypophosphatemia, normocalcemia, and elevated $1,25(OH)_2$ vitamin D
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	• *CLDN16* and *CLDN19*	AR	• Hypomagnesemia, nephrocalcinosis, and progression to ESRD in adolescence
Distal renal tubular acidosis	• *ATP6V1B1*, *ATP6V0A4*, and *SLC4A1*	AD	• Hypokalemia, metabolic acidosis, nephrocalcinosis, growth delay, early-onset sensorineural deafness, and metabolic bone disease
Primary hyperoxaluria	• *AGXT*, *GRHPR*, and *HOGA1*	AR	• CKD with progression to ESRD and risk of systemic oxalosis
Infantile hypercalcemia	• *CYP24A1* and *SLC34A1*	AR	• Hypercalcemia
Cystinuria	• *SLC3A1* and *SLC7A9*	AR or AD	• Cystine stones and nephrocalcinosis
Hereditary hyperuricosuria	• *HPRT1*	XLR	• Hyperuricemia, neurologic deficits (psychomotor delay, intellectual disability), and renal failure
Hereditary xanthinuria	• *XDH*, *MOCOS*, *MOCS1*, *MOCS2*, and *GPHN*	AR	• Myopathy, psychomotor deficit, growth delay, seizure, and hypotonia
Adenine phosphoribosyltransferase deficiency	• *APRT*	AR	• Crystalluria and progressive CKD

AD, autosomal dominant; AR, autosomal recessive; CKD, chronic kidney disease; ESRD, end-stage renal disease; LMW, low molecular weight; PTH, parathyroid hormone; XLR, X-linked recessive.

inhibitors have been shown to be efficacious in adult Bartter syndrome [42].

Bartter syndrome type III is a result of biallelic mutations in *CLCNKB*, encoding the voltage-gated Cl channel protein ClC-Kb. This type is characterized by onset during the pre-adult years or later due to hypokalemic alkalosis, hypercalciuria, and nephrocalcinosis [43]. Management of type III is focused on the replacement of electrolytes, especially magnesium and potassium.

Bartter syndrome type IVa is characterized by sensorineural hearing loss and early-onset chronic kidney disease (CKD) and is attributed to biallelic mutations in the gene encoding Barttin (*BSND*), a chaperone protein for the chloride-channel proteins ClC-Ka and ClC-Kb [44]. The recognizable feature of deafness is provoked by the expression of Barttin in potassium-secreting marginal cells located in the scala media [45]. Uncommon biallelic mutations in *CLCNKB* and the adjacent *CLCNKA* encoding

ClC-Ka result in the phenotype referred to as Bartter syndrome type IVb [46].

Bartter syndrome type V is referred to as a transient antenatal Bartter syndrome with an X-linked recessive trait. Type V is due to hemizygous mutations in *MAGED2*, encoding the melanoma-associated antigen D2, a protein that regulates the cell cycle [47]. While Bartter syndrome types I to IV show autosomally recessive inheritance, Bartter syndrome types V and VI are autosomal dominant and X-linked recessive traits, respectively [35,39].

Management strategies are mainly supportive and include non-steroidal anti-inflammatory drugs that reduce renal prostaglandin production and spironolactone that inhibits distal tubular Na^+–K^+ exchange to correct hypokalemic metabolic alkalosis [48].

3.1.3. Dent disease and Lowe syndrome

Dent disease is an X-linked recessive disorder expressed in males and is categorized into types 1 and 2. Type 1 is associated with loss-of-function mutations in *CLCN5* (Xp11.22), whereas type 2 is associated with mutations in *OCRL* (Xq25) [49,50]. Lowe syndrome is a severe phenotype of Dent disease, characterized by hypercalciuria and cataracts, renal anomalies, and nephrocalcinosis [43,51,52]. The genetic underpinnings of Dent disease are unknown in 25% of patients. Dent disease is diagnosed by increased low-molecular-weight proteinuria, hypercalciuria, and at least one of the following features: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia, and/or gradual deterioration in renal function causing end-stage renal disease (ESRD) [53,54]. Low-molecular-weight proteinuria is evident in most patients and can be detected by measuring the level of retinol-binding protein, α1-microglobulin, or β2-macroglobulin. Notably, the presence and magnitude of nephrocalcinosis are not associated with the risk of ESRD [52]. While the development of urolithiasis is considered to be regulated by hypercalciuria in Dent disease, how hypercalciuria develops in these patients is unclear [55]. Extrarenal manifestations of Dent disease include rickets and osteomalacia, which are commonly observed [54].

Dent disease type 1 is associated with mutations of *CLCN5* encoding the electrogenic chloride-hydrogen exchange transporter 5. In turn, reabsorption of solute is decreased in the proximal tubule due to defective Cl^- flow and subsequent disruption of endosomal acidification and trafficking to the apical surface [56]. In Dent disease type 2, *OCRL* encodes inositol polyphosphate 5-phosphatase and is involved in vesicle trafficking, phagocytosis, cell adhesion and migration, cytokinesis, cellular polarity, and intracellular signaling [57]. *OCRL* mutations can present as Dent disease type 2 if only the kidney is affected or as Lowe syndrome if there are other extrarenal phenotypes, including delayed development and cataracts. Among various renal manifestations, nephrocalcinosis is common (40%) in Dent disease type 2, while renal failure is more frequent in Lowe syndrome [58].

The management of Dent disease is mainly supportive, with the goals of decreasing hypercalciuria and relieving the risks of urolithiasis and renal function deterioration. Low-sodium dietary measures and thiazides are recommended with close monitoring of electrolyte levels [59]. In a retrospective study of 109 males with *CLCN5* mutations and nine patients with a mutation of the *OCRL* gene, high-dose thiazide diuretics reduced the excretion of urine calcium [59]. Affected individuals may still develop kidney failure and require dialysis or kidney transplantation [58].

3.1.4. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)

HHRH is an uncommon disorder with an autosomal recessive inheritance pattern. It is exerted by biallelic mutations in *SLC34A3*, encoding the Na^+-dependent phosphate transport protein 2C. Monoallelic *SLC34A3* variants can induce urolithiasis with idiopathic hypercalciuria irrespective of a decrease in bone mineral density [27,60]. HHRH is characterized by rickets, hypophosphatemia, decreased reabsorption of renal phosphate, hypercalciuria with normocalcemia, and elevated renal production of 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) [24]. Elevated $1,25(OH)_2D$ induces hypercalciuria by increased absorption of calcium and phosphorus from the intestines, increased mobilization from bone, increased reabsorption of calcium, and reduced reabsorption of phosphorus due to inhibition of parathyroid hormone secretion [24]. Renal phosphate depletion and hypophosphatemia can inhibit fibroblast growth factor 23 (FGF23), which stimulates catabolism of $1,25(OH)_2D_3$. Low levels of FGF23 and hypophosphatemia decrease the expression of cytochrome P450 family 24 subfamily A member 1 and subsequently induce hypersensitivity to vitamin D [61]. Therefore, the management of HHRH should involve oral phosphorus supplementation and restraint of vitamin D analog supplementation. The efficacy of oral phosphorus in reducing the risk of urolithiasis and loss of bone density has not been elucidated [62].

3.1.5. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)

FHHNC is a rare autosomal recessive disorder due to mutations in the *CLDN16* or *CLDN19* genes encoding the proteins claudin-16 and claudin-19, respectively [63]. More than 40 missense mutations in *CLDN16* that affect the first extracellular loop of the protein have been characterized. Notably, a few of these mutations have been found to be associated with self-limited hypercalciuria without significant abnormalities of magnesium or renal function deterioration during childhood [64]. Biallelic *CLDN16* (3q27) mutations induce FHHNC alone, while individuals carrying *CLDN19* mutations commonly exhibit associated congenital ocular defects resulting in variable visual impairments [63,65]. A positional cloning study also reported that mutations in paracellin-1 (*PCLN-1*) induce renal magnesium wasting. *PCLN-1* is found in tight junctions of the thick ascending limb of Henle and is associated with the claudin family of tight junction proteins [65].

FHHNC is featured by the wasting of calcium and magnesium, and subsequent hypercalciuria, hypomagnesemia, nephrocalcinosis, and progressive CKD [66]. Most individuals experience symptoms in young adulthood. Symptoms include seizures or tetany due to hypomagnesemia or hypocalcemia [65]. Other than hypomagnesemia, hypercalciuria, and nephrocalcinosis, which are always present, individuals can also present with polydipsia and polyuria,

incomplete dRTA, hyperuricemia, hypocitraturia, and tooth enamel defects [66—68].

Renal biopsies are rarely useful for this disorder, and the diagnosis of FHHNC is challenging in pediatric patients presenting with a history of recurrent urolithiasis and renal insufficiency. Hypokalemic metabolic alkalosis is not evident in FHHNC, differentiating this disorder from Bartter syndrome. Usually, a diagnosis is based on the identification of biallelic *CLDN16* or *CLDN19* mutations.

While there is no definite management for FHHNC, supplementation with high-dose magnesium and administration of thiazide diuretics have been proposed as strategies to decrease the excretion of urine calcium. However, thiazides can not significantly decrease the excretion of urine calcium or postpone the onset and progression of CKD [13,68]. Indomethacin, which inhibits prostaglandin production, has also been suggested as a therapeutic as prostaglandin E2 suppresses the reabsorption of thick ascending limb of Henle. However, there is limited evidence concerning the efficacy of this management strategy [69]. Vitamin D supplements must be administered cautiously since they can exacerbate hypercalciuria [66].

3.1.6. Hereditary dRTA

Primary dRTA is commonly observed at a young age and is characterized by impairment of tubular secretion of hydrogen ions in the distal nephron and subsequent metabolic acidosis [70]. Hypokalemia resulting from renal potassium wasting, hypercalciuria with nephrocalcinosis, and metabolic bone disease are commonly associated with dRTA [13]. Hereditary dRTA is usually diagnosed during infancy based on growth delay. Late-onset presentations are more commonly related to monoallelic *SLC4A1* mutations that induce red blood cell abnormalities [71].

Hereditary dRTA is inherited in an autosomal recessive manner when caused by pathogenic variants in *ATP6V0A4*, *ATP6V1B1*, *FOXI1*, or *WDR72*, or in an autosomal dominant or autosomal recessive manner when caused by pathogenic variants in *SLC4A1*. Biallelic mutations are noted in up to 80% of affected patients [72,73]. *ATP6V1B1* and *ATP6V0A4* encode subunits B1 and A4, respectively, of the hydrogen-ATPase pump in α-intercalated cells [74,75]. Although deafness is uncommon with *ATP6V0A4* mutations, hearing loss is observed in some affected individuals during young adulthood [76,77]. *SLC4A1* is present on chromosome 17q21.31 and encodes the chloride-bicarbonate exchanger AE1 that is expressed on the basolateral membrane of α-intercalated cells. AE1 also regulates chloride and bicarbonate exchange on erythrocyte membranes; polycythemia is occasionally noted in affected individuals [78]. While *TP6V1B1* and *FOXI1* mutations are seen in early-onset hearing loss, mutations in *ATP6V0A4* can result in late-onset deafness [77,79].

The dRTA should be suspected in the presence of hyperchloremic metabolic acidosis with normal renal function. Symptoms include polydipsia, polyuria, emesis, constipation, loose stool, loss of appetite, and nephrocalcinosis due to persistently alkaline urine [77,80]. Metabolic acidosis can result in bone calcium loss and subsequent hypercalciuria, which can induce nephrocalcinosis [71].

The management of dRTA is focused on the correction of metabolic acidosis with twice-daily oral potassium citrate. This can protect bone health by increasing urine citrate and decreasing urine calcium excretion. Nevertheless, persistent alkaline urine cannot be altered, and patients are at high risk for calcium phosphate urolithiasis as well as nephrocalcinosis [71].

3.1.7. Primary hyperoxaluria

Primary hyperoxaluria is an autosomal recessive disorder characterized by aberrations in glyoxylate metabolism and subsequent hepatic overproduction and excretion of urine oxalate. Excess excretion of urine oxalate increases the risk of calcium oxalate crystal formation and nephrocalcinosis [81]. There are three distinct types of primary hyperoxaluria depending on the enzymes involved in the oxalate metabolic pathway [82].

Primary hyperoxaluria type 1 is caused by biallelic mutations in the liver-specific alanine-glyoxylate and serine-pyruvate aminotransferase (*AGXT*) gene. Approximately 80% of all primary hyperoxaluria cases are due to mutations in *AGXT*, which produces the most severe form. ESRD occurs in approximately 60% of individuals by the age of 40 years [81]. Decreased activity of alanine-glyoxylate aminotransferase induces glyoxylate accumulation through impaired conversion of glyoxylate to glycine, resulting in increased oxalate and glycolate production [83]. The p.Gly170Arg mutation is the most common among the 200 *AGXT* mutations identified to date. Affected individuals that are heterozygous for the p.Gly170Arg mutation have a greater risk of having severe disease and respond less to pyridoxine (vitamin B6). In contrast, individuals that are homozygous for this mutation present with milder disease and usually respond well to pyridoxine [81,84—86]. Patients with other mistargeting mutations in *AGXT*, including p.Gly41Arg, are also candidates for treatment with pyridoxine [87]. For patients in whom renal transplantation is indicated, combined liver transplantation can be considered since this will help correct metabolic abnormalities [88].

Primary hyperoxaluria type 2 is due to mutations in the glyoxylate and hydroxypyruvate reductase gene (*GRHPR*), which encodes glyoxylate reductase/hydroxypyruvate reductase (GR/HPR). Without GR/HPR, glyoxylate is metabolized to oxalate, and hydroxypyruvate is metabolized to L-glycerate; thus, affected individuals have increased oxalate and L-glycerate excretion [89,90]. Primary hyperoxaluria type 2 accounts for approximately one-tenth of all reported cases of primary hyperoxaluria. In general, individuals with primary hyperoxaluria type 2 have relatively lower urinary oxalate excretion than those with type 1, in addition to a milder phenotype. Type 2 is characterized by a slower progression to ESRD compared to type 1; still, progression to ESRD occurs in 18% of patients [81].

Primary hyperoxaluria type 3 is due to mutations in 4-hydroxy-2-oxoglutarate aldolase 1 (*HOGA1*). *HOGA1* catalyzes the cleavage of 4-hydroxy-2-oxoglutarate (HOG) to pyruvate and glyoxylate; the consequent accumulation of HOG inhibits the function of GR/HPR [81]. Type 3 constitutes 10% of primary hyperoxaluria and is the least likely type to progress to ESRD [81]. Presentation is as early as 2.6 years; however, only 4% of affected individuals progress to ESRD.

Management of primary hyperoxaluria with oral oxalate restriction has limited efficacy. Urine calcium oxalate crystallization inhibitors in addition to sufficient fluid intake can be efficacious [91].

3.1.8. Infantile hypercalcemia

Infantile hypercalcemia type 1 is caused by biallelic mutations in *CYP24A1*, which have also been reported in families with severe hypercalcemia following vitamin D supplementation and in adults with hypercalcemia and hypercalciuria [24]. The inhibition of vitamin D synthesis with fluconazole or ketoconazole has been shown to be effective in patients with hypercalcemia and nephrolithiasis [92].

Infantile hypercalcemia type 2 is associated with biallelic *SLC34A1* mutations, and renal phosphate wasting results in increased production of $1,25(OH)_2D_3$ [24]. *SLC34A1* encodes Na^+-dependent phosphate transport protein 2A; its loss in patients with HCINF-2 results in proximal tubular renal phosphate wasting, hypophosphatemia, and compensatory increases in $1,25(OH)_2D$, which induce hypercalcemia and hypercalciuria. Such patients can be treated with phosphate supplementation in order to normalize serum phosphate levels and to prevent FGF23 suppression, which leads to disruptions in vitamin D and calcium metabolism [93].

3.2. Non-calcium nephrolithiasis disorders

3.2.1. Cystinuria

Cystinuria arises as a result of defective amino acid transport in the proximal tubule and is the most commonly identified hereditary disorder associated with urolithiasis formation, accounting for approximately 5%–10% of all pediatric cases and 1% of adult urolithiases cases [94,95]. Individuals with classical recessive cystinuria have inherited two mutations in the solute carrier family 3 member 1 (*SLC3A1*) gene located on chromosome 2, which encodes the heavy subunit rBAT of the transport mechanism. Individuals with the dominant form of cystinuria have inherited two mutations in the solute carrier family 7 member 9 (*SLC7A9*) gene on chromosome 19, which encodes the transport channel itself. Mutations of these proteins impair the reabsorption of cysteine and dibasic amino acids including arginine, lysine, and ornithine, resulting in increased excretion [96,97]. rBAT and $b^{0,+}$AT proteins form heterodimers via a disulfide bridge to make up the $b^{0,+}$AT amino acid transport system [1]. Cystinuria is characterized by frequent recurrences because cysteine is less soluble in urine [94]. Patients with cystinuria are prone to CKD progression due to recurrent urolithiasis and obstructive uropathy.

Management of individuals with cystinuria focuses mainly on prevention, as these patients are likely to receive multiple urological interventions. Management strategies include aggressive fluid intake and low sodium and protein intake, aimed at decreasing the consumption of the cystine precursor methionine. Urinary alkalinization can be performed to reduce cystine stone formation. The goal of sodium bicarbonate and/or potassium citrate treatment is to increase urinary pH to above 7.0 in order to maintain the solubility of the amino acid cystine. Acetazolamide has shown benefits in increasing urinary pH in patients on potassium citrate. However, precautious measures should be taken in regard to calcium phosphate stone formation. Thiol-binding agents including D-penicillamine and tiopronin can also be used to enhance the solubility of urinary cystine. These agents decrease cystine concentration through the formation of cysteine-agent dimers [98].

3.2.2. Hereditary hyperuricosuria

Hereditary hyperuricosuria is due to partial or complete deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase, which is encoded by *HPRT1* [99]. Lesch-Nyhan syndrome is an X-linked recessive disorder due to complete deficiency of this enzyme and is characterized by hyperuricemia, hyperuricosuria, uric acid stones, and neurological deficits such as psychomotor deficit, intellectual disability, and childhood renal failure [99]. Partial loss-of-function mutations in *HPRT1* can result in milder symptoms. The mildest phenotype, referred to as Kelley-Seegmiller syndrome, typically presents as uric acid urolithiasis. Mutations in *PRPS1* cause hyperuricemia, hyperuricosuria, gout, hearing loss, uric acid urolithiasis, and intellectual disability [100,101]. Loss-of-function mutations in *SLC22A12* or *SLC2A9* encoding the proximal tubular uric acid reabsorption transporters urate anion exchanger 1 and glucose transporter type 9, respectively, are also related to excessive uric acid excretion and subsequent formation of nephrolithiasis [102].

Treatment with xanthine oxidase inhibitors, including allopurinol or febuxostat, has been shown to be promising by reducing hyperuricemia and hyperuricosuria. However, precautions should be taken since hyperxanthinuria and hypoxanthinuria can occur in patients with complete hypoxanthine-guanine phosphoribosyltransferase deficiency [99]. Moreover, urine alkalinization can be performed to enhance the solubility of uric acid, along with aggressive fluid intake [103,104].

3.2.3. Hereditary xanthinuria

Hereditary xanthinuria has an autosomal recessive inheritance due to impairment of purine metabolism. Type 1 xanthinuria is associated with mutations in *XDH*, encoding xanthine dehydrogenase-oxidase (XDH), while type 2 xanthinuria is associated with mutations in *MOCOS*, encoding molybdenum cofactor sulfurase, a cofactor in XDH and aldehyde oxidase activation [105,106]. XDH or molybdenum cofactor sulfurase deficiency causes a decrease in serum uric acid concentration and high concentrations of xanthine and hypoxanthine, which are the precursors of oxypurine. Type 2 xanthinuria causes an elevated concentration of serum sulfite, allowing differential diagnosis from type 1 xanthinuria [107]. Type 1 xanthinuria can be silent or manifest as myopathy, while type 2 is featured by psychomotor deficits, growth delay, seizures, and hypotonia due to increased levels of sulfites [107,108]. Xanthine urolithiasis is observed in approximately one-third of affected individuals. Diets low in purine and aggressive fluid intake can help protect against the formation of xanthine stones [1].

3.2.4. Adenine phosphoribosyltransferase (APRT) deficiency

APRT deficiency is a rare inborn error of purine metabolism due to homozygous or compound heterozygous biallelic *APRT* mutations. APRT deficiency leads to the accumulation of the compound 2,8-dihydroxyadenine (DHA), which causes DHA stone formation due to high insolubility. Urolithiasis is commonly observed in individuals with APRT deficiency. While secondary progressive CKD can result from crystalline nephropathy, approximately one-fifth of the individuals are known to present with ESRD due to tubulointerstitial injury caused by crystal deposition or obstruction [53,109,110].

Patients with APRT deficiency can be diagnosed by detection of DHA in stone analysis, elevated urine 2,8-DHA crystals, renal biopsy, or absence of red blood cell APRT activity [95]. Urinary DHA crystals are radiolucent, and caution is needed to differentiate this disorder from uric acid urolithiasis. Under light microscopy and polarized light microscopy, DHA crystals often feature a central Maltese cross pattern. Moreover, both calcium oxalate and DHA crystals are birefringent, and thus differential diagnosis should include APRT deficiency and primary hyperoxaluria [93,109,110].

Allopurinol or febuxostat, which is xanthine oxidase inhibitors, can decrease 2,8-DHA synthesis and reduce the risk of urolithiasis formation and progression of crystal nephropathy [110,111]. Of note, xanthine oxidase inhibitor therapy should be continued in renal allograft patients as APRT deficiency is prone to recurrence without maintenance [95].

4. Clinical implications

Monogenic causes of urolithiasis are commonly overlooked in recurrent stone-formers [27—29]. Moreover, classical phenotypes might not be evident in all stone-formers, hindering an appropriate diagnosis [29,112]. Underdiagnosis of monogenic disorders can result in suboptimal treatment strategies and lead to multiple surgical interventions that can decrease quality of life and renal function. Patients who present at an early age and those with recurrent and bilateral stones, familial history, or parental consanguinity should be suspected of a hereditary component of urolithiasis and be considered candidates for genetic counseling [6]. In these patients, a multidisciplinary approach between clinicians and geneticists that involves biochemical and genetic testing should be adopted to develop optimal management strategies. This is especially important in pediatric patients who have a higher likelihood of a monogenic diagnosis than adults; whole-exome sequencing should be considered [29]. Results from dietary studies have indicated that dietary intake patterns can be heritable, and prospective interventions should include dietary modifications. Unraveling hereditary traits in recurrent stone-formers remains a challenge; however, genome-guided precision medicine approaches can advance the development of optimal management strategies for these patients. Such advancements may facilitate the development of individualized medical therapies based on polygenic genotypes in recurrent idiopathic stone formers.

5. Conclusion

The pathophysiology underlying urolithiasis formation is complex and multifactorial, but evidence strongly suggests the existence of a genetic predisposition. Contemporary genomic techniques have identified numerous monogenic causes of urolithiasis in humans. However, the frequency of monogenic causes of urolithiasis relative to the total population remains undetermined. A better understanding of the genetic etiology of the disorder in terms of genome-guided precision medicine is needed, which will facilitate targeting of the relevant biological pathway. Moreover, it is unknown why affected patients with the same metabolic abnormalities exhibit more severe disease than other patients. Further comprehensive genetic studies using combined proteomic, chemistry, and biochemistry approaches are needed to clearly identify heritable causes of urolithiasis and establish centralized registries for future clinical studies. Such measures will allow for novel personalized diagnostic, therapeutic, and prophylactic approaches for recurrent urolithiasis formers.

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

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