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Monogenic causation of pediatric nephrolithiasis

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Nephrolithiasis is a condition in which crystals precipitate out of the urine forming kidney stones in the renal calyces and pelvis. Approximately 80% of stones are composed of calcium oxalate and calcium phosphate. In recent years, there has been a significant increase in the prevalence of nephrolithiasis across populations, specifically in that of the pediatric population. The etiology of stone disease is multifactorial, and includes environmental, dietary, hormonal, and genetic factors. Evidence for monogenic causation (also known as Mendelian or single-gene disorders) in nephrolithiasis includes the finding that 30% of children with stone disease report a positive family history, with monogenic nephrolithiasis accounting for approximately 30% of cases. Monogenic nephrolithiasis can occur in isolation or may be the result of an underlying genetic disorder including autosomal dominant hypocalcemia (ADH), primary hyperoxalurias, and hereditary hypophosphatemic rickets with hypercalciuria (HHRH), to name a few. Currently, there are 41 known genes that represent monogenic causes of human nephrolithiasis. Since early detection of these mutations can in some cases prevent the progression to end stage kidney disease in pediatric patients, establishing the genetic basis for nephrolithiasis is increasingly important. Here we provide an overview of kidney stone disease in children with a focus on monogenic causation in the pediatric population.

KEYWORDS

nephrolithiasis, kidney stones, monogenic, pediatric, genetic, kidney disease

Introduction

Nephrolithiasis is a common condition in which crystals of mineral concentrations precipitate out of the urine, forming kidney stones in the renal calyces and pelvis (1). There are four main distributions of compositions of kidney stones; 80% of stones are composed of calcium oxalate and calcium phosphate, 8-10% are uric acid stones, 7-8% are struvite stones, and about 2-5% are cysteine stones (2). The most common stone formation, calcium oxalate, begins with nucleation, crystal growth and then crystal

aggregation to ultimately form a stone (3). There are many factors which influence the development of nephrolithiasis. Some are promoters of calcium supersaturation including high urinary excretion of calcium, oxalate, urate, and low urine volume; others are inhibitors of stone formation including citrate, magnesium and potassium (4). Patients diagnosed with nephrolithiasis typically present with abdominal and flank pain, fever and chills, nausea and vomiting, hematuria, dysuria, and urinary frequency (5). Common diagnostic techniques include computed tomography (CT), ultrasonography, and urinalysis (5). Treatment options for both adults and children include pain management, urinary decompression if secondary obstruction is present, medical expulsion therapy, ureteroscopy, and extracorporeal shockwave lithotripsy (6). Patients with nephrolithiasis also have an increased risk of both chronic kidney disease (CKD) and end stage kidney disease (ESKD) (7). Somewhat surprising is that even asymptomatic kidney stone patients are at a higher risk of developing ESKD (7). This elevated risk of CKD and ESKD has prompted the increased use of genetic evaluation to facilitate in the diagnosis, specific treatment strategies, and ultimately preventing recurrence of stone disease (7). The added benefit of establishing a genetic diagnosis in pediatric patients is that it can lead to early disease detection, provide a definitive molecular diagnosis, inform prognosis in both patients and potentially affected family members (8).

Prevalence of kidney stone disease

Kidney stone disease is common worldwide, with an ever-increasing prevalence. In the last decade, 1 in 10 people in the United States report a history of nephrolithiasis, compared to 1 in 20 individuals in 1994 (9). One of the most prominent increases in nephrolithiasis incidence over the past few decades has occurred in the pediatric population (10). Studies in the United States have reported a yearly increase in incidence in nephrolithiasis from 1984 to 1990 of 7.2 per 100,000 children under the age of 18, and 14.5 per 100,000 from 2003 to 2008 with an all-time high of 65.2 cases per 100,00 children in 2011 (10, 11). It is predicted that the prevalence of this disease will continue to increase in all populations, including the pediatric population.

Pathophysiology of kidney stones

Kidney stones are solid masses with sizes that vary from a grain of sand to a pearl and can be either yellow or brown in color (12). Kidney stones arise from a positive imbalance in urinary promoters and inhibitors of crystallization, causing supersaturation leading to crystallization (13). The stages of formation are as follows: crystal nucleation begins with solute molecules becoming clustered in solvent (12). Supersaturation then occurs, followed by crystal growth by encrustation once a nucleus is present, and finally agglomeration of the stone (Figure 1) (12). There are four different forms of kidney stones: 1) calcium oxalate and phosphate (80%), 2) uric acid (8-10%), 3) struvite stones (7-8%), and 4) cysteine stones (2-5%) (2). Calcium nephrolithiasis is the most common stone type, with calcium oxalate significantly more prevalent than calcium phosphate stone formation (15). Calcium oxalate stones grow and form at Randall's plaques which are lesions that seem to provide the platform for calcium oxalate crystal formation (Figure 1) (15). Hypercalciuria, excess calcium in urine, is one of the most important pathophysiological factors for the development of calcium nephrolithiasis (15). When calcium is in abundance, it increases the ionic activity and saturation of the crystalizing salts; oxalate and phosphate, while binding to stone inhibitors (15). This same effect can also be caused by high dietary salt (16). Hypercalciuria is mainly caused by systemic acidosis, since chronic acidosis leads to renal calcium leak, and excess protein load (15). Hypocitraturia often goes hand in hand with hypercalciuria, as citrate complexes with calcium and prevents stone growth, therefore a lack of citrate permits calcium oxalate and phosphate stones (17). It has also been reported that hyperoxaluria causes calcium oxalate stones by increasing the concentration of calcium oxalate in urine (17). Uric acid nephrolithiasis, which is less common, is caused by hyperuricosuria, acidic pH, or a combination of the two (15). Struvite stones, or "infection stones", are not caused by metabolic deficiency, but rather urease-positive microorganisms which produce ammonium and bicarbonate which causes struvite crystallization (15). The final type, cysteine nephrolithiasis, is mainly caused by genetic defects, although each stone types may have underlain genetic causation (15).

Risk factors for kidney stones

Factors hypothesized to contribute to this rise in nephrolithiasis prevalence include dietary habits, medications, and global warming (18). Many other risk factors are also at an all-time high, and include obesity, diabetes, hypertension, and metabolic syndrome (3). Obesity and diabetes alone increase the risk of developing nephrolithiasis by 55% and 59%, respectively (9). Researchers have discovered that nutritional exposure is one of the most important factors in the increase in prevalence of nephrolithiasis (3). Recent trends have shown that the reduction of intake of fluids, calcium, and fruit intake, as well as an increase in dietary sodium, meat and high oxalate-containing foods are all major contributors in the development of nephrolithiasis (3). Managing these nutritional factors is crucial for nephrolithiasis management and prevention, along with prevention of systemic and cardiovascular comorbidities (3). Various medications including antibiotics, diuretics, laxatives, carbonic anhydrase

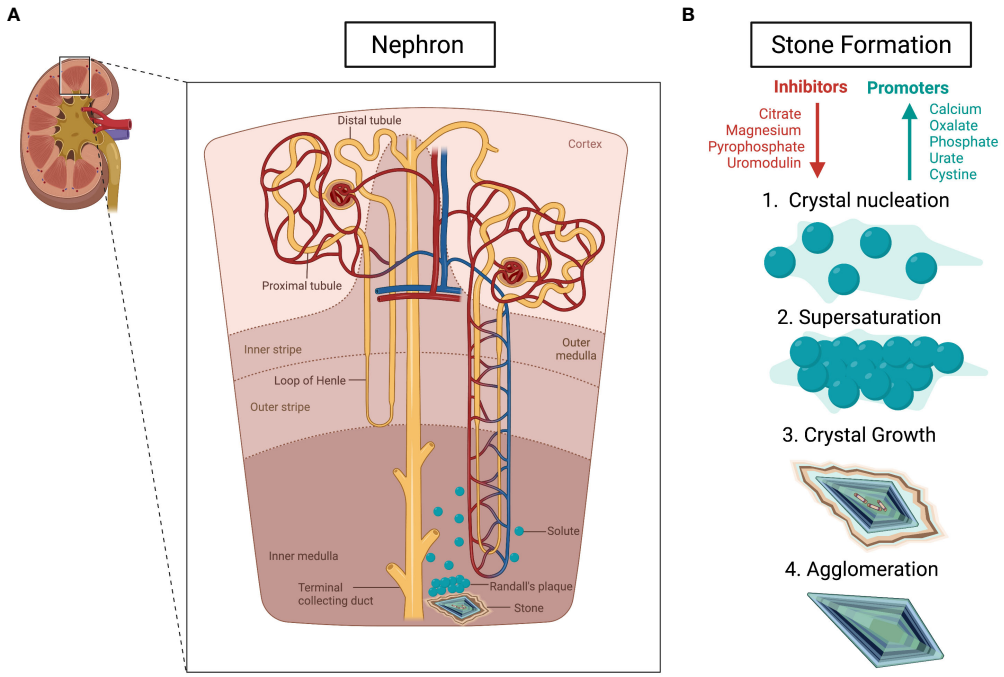

FIGURE 1
Pathophysiology of kidney stones. **(A)** The development of kidney stones through Randal's plaque in the nephron. **(B)** The steps of kidney stone formation, beginning with an imbalance of inhibitors (shown in red) and promoters (shown in blue). The arrows represent an increase (blue) and decrease (red). Created using BioRender.com (14).

inhibitors, ephedra alkaloids, potassium channel blockers, reverse transcriptase inhibitors, sulfonylureas, and others, also pose a risk in nephrolithiasis development and recurrence (5). Because nephrolithiasis has a 50% 5-year recurrence establishing a definitive diagnosis and targeting potential modifiable risk factors is vital to avoid recurrence of disease (19).

Evidence for genetic causation in kidney stone disease

Although kidney stone formation can be caused by environmental, dietary, and hormonal factors as outlined above, another significant contributor is genetics. There is strong evidence that nephrolithiasis aggregates in families; indeed, there is a 3-fold increase in incidence when there is a positive family history (20). Data suggest that 35-60% of patients with stone disease have a family history (20). Twin studies have shown that there is a 45% heritability factor for developing nephrolithiasis (21). The family clustering index for nephrolithiasis is 2.5-4 (20, 22). This is comparable to other diseases with a strong evidence of genetic background including diabetes and hypertension, both which have a heritability factor of 2 (23). Dietary habits including a high sodium diet and decreased fluid intake are other risk factors for developing nephrolithiasis (3). Studies have shown that diet, which was thought to be mainly attributed to environmental causation, also has a heritability of 65% for meal size and 44% for meal frequency, thereby linking diet to genetics (24).

Studies show that pathogenic, single gene mutations account for a high proportion of kidney stone disease in childhood (18). For example, Daga demonstrated that among a cohort of patients who presented with kidney stones before the age of 25, exome sequencing detected a monogenic causative mutation in 15 of 51 patients (29.4%) (18). Another study conducted by Huang, detected monogenic causative mutations using exome sequencing in 24 of 32 cases (75%) (25). The majority (80%) of patients with monogenic stone disease carry recessive mutations and most have disease onset before the age of 10 years (18). Currently, there are 41 known genes that represent monogenic causes of human nephrolithiasis (Table 1). Yucheng found that between 17-29% of cases of childhood onset kidney stones are due to mutation in one of these known kidney stone genes (65). However, the heritability factor for nephrolithiasis is over 45% suggesting that a higher that reported proportion of kidney stones are due to single gene disorders in yet to be discovered genes (21).

TABLE 1 Genes causing monogenic human nephrolithiasis. Related monogenic nephrolithiasis disorders also provided.

Gene	Protein	Reference	Mode of inheritance	Related Disease
AGXT	Alanine-glyoxylate aminotransferase	Purdue *Proc Natl Acad Sci U S A* 88:10900, 1991 (26)	AR	Primary hypouricemia, Primary Hyperoxaluria
ALDOB	Aldolase B fructose biphosphate	Paolella *Hum Genet* 77:115, 1987 (27)	AR	Fructose intolerance
ALPL	Alkaline Phosphatase, Liver	Weiss *Proc Natl Acad Sci U S A* 85:7666, 1988 (28)	AR	Hypophosphatasia
APRT	Adenine phosphoribosyltransferase	Hidaka *J Clin Invest* 80:1409, 1987 (29)	AR	Dihydroxyadeninuria
ATP6V0A4	ATPase, H+ transporting, lysosomal V0 subunit a4	Smith *Nat Genet* 26:71, 2000 (30)	AR	Primary distal renal tubular acidosis
ATP6V1B1	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1	Karet *Nat Genet* 21:84, 1999 (31)	AR	Primary distal renal tubular acidosis
ATP7B	ATPase, Cu(2+)-transporting, beta polypeptide	Gromadzka *Clin Genet* 68:524, 2005 (32)	AR	Wilson Disease
CA2	Carbonic anhydrase II	Venta *AJMG* 49:1082, 1991 (33)	AR	Osteoporosis, autosomal recessive 3, with renal tubular acidosis
CLCNKB	Chloride channel, voltage-sensitive Kb	Simon *Nat Genet* 17:171, 1997 (34)	AR	Bartter Syndrome
CLDN16	Claudin 16	Simon *Science* 285:103, 1999 (35)	AR	Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis
CLDN19	Claudin 19	Konrad AJHG 79:949, 2006 (36)	AR	Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis
CTNS	Cystinosin	Town *Nat Genet* 18:319, 1998 (37)	AR	Cystinosis
CYP24A1	Cytochrome P450, family 24, subfamily A, polypeptide 1	Schlingmann *NEJM* 36:410, 2011 (38)	AR	Infantile Idiopathic Hypercalcemia
FAH	Fumarylacetoacetate hydrolase	Aponte Proc Nat Acad Sci 98:641, 2001 (39)	AR	Tyrosinemia
FAM20A	Family with sequence similarity 20, member A	Jaureguiberry *Nephron Physiol* 122:1, 2012 (40)	AR	Amelogenesis Imperfecta Type IG
G6PC	Glucose 6 phosphate catalytic	Seydewitz *Hum Mutat* 15:115, 2000 (41)	AR	Glycogen storage disease
GRHPR	Glyoxylate reductase/hydroxypyruvate	Cramer *Hum Mol Genet* 8:2063, 1999 (42)	AR	Primary Hyperoxaluria
HOGA1	4-hydroxy-2-oxoglutarate aldolase 1	Belostotsky *AJHG* 87:392, 2010 (43)	AR	Primary Hyperoxaluria
KCNJ1	Potassium inwardly rectifying channel, subfamily J, member 1	Simon *Nat Genet* 14:152, 1996 (34)	AR	Bartter Syndrome 2, Hypercalciuria
KCNJ10	Potassium Channel inwardly rectifyinh subfamily J, member 10	Bockenhauer *NEJM* 360:1960, 2009 (44)	AR	SESAME syndrome
SLC12A1	Solute carrier family 12, member 1	Simon *Nat Genet* 13:183, 1996 (34)	AR	Bartter Syndrome 1, Hypercalciuria
SLC26A1	Solute carrier family 26 (sulfate transporter), member 1	Gee *AJHG* 98:1228, 2016 (45)	AR	Hyperoxaluria and Hepatotoxicity
SLC2A2	Solute carrier family 2 (faciliated glucose transporter)	Akagi *J Hum Genet* 45:60, 2000 (46)	AR	Fanconi-Bickel Syndrome
SLC34A3	Solute carrier family 34 (sodium	Lorenz-Depiereux *AJHG* 78:193, 2006 (47)	AR	Hereditary Hypophosphatemic Rickets with Hypercalciuria
XDH	Xanthine dehydrogenase	Ichida *J Clin Invest* 99:2391, 1997 (48).	AR	Xanthinuria
HNF4A	Hepatocyte nuclear factor 4, alpha	Hamilton *J Med Genet* 51:165, 2014 (49)	AD	Fanconi Renotubular syndrome 4

(Continued)

TABLE 1 Continued

Gene	Protein	Reference	Mode of inheritance	Related Disease
SLC9A3R1	Solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 1	Karim *NEJM* 359:1128, 2008 (50)	AD	Hypophosphatemic nephrolithiasis and osteoporosis 2
CASR	Calcium-sensing receptor	Pearce *NEJM* 335:1115, 1996 (51)	AD/AR	Autosomal Dominant Hypocalcemia,with Bartter Syndrome, Familial Hypocalciuric Hypercalcemia
SLC22A12	Solute carrier family 22	Enomoto *Nature* 417:447, 2002 (52)	AD/AR	Renal Hypouricemia
SLC2A9	Solute carrier family 2	Matsuo *AJHG* 83:744, 2008 (53)	AD/AR	Renal Hypouricemia
SLC34A1	Solute carrier family 34	Prie *NEJM* 347:983, 2002 (54)	AD/AR	Fanconi renotubular syndrome 2, hypercalemia
SLC3A1	Solute carrier family 3, member 1 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport	Calonge *Nat Genet* 6:420, 1994 (55)	AD/AR	Cystinuria
SLC4A1	Solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane)	Bruce J Clin Invest 100:1693, 1997 (56)	AD/AR	Primary distal renal tubular acidosis
SLC7A9	Solute carrier family 7 (glycoprotein associated	Feliubadalo *Nat Genet* 23:52, 1999 (57)	AD/AR	Cystinuria
VDR	Vitamin D (1,25- dihydroxyvitamin D3) receptor	Scott *JASN* 10:1007, 1999 (58)	AD/AR	Rickets
CLCN5	Chloride channel, voltage-sensitive 5	Lloyd *Nature* 379:445, 1996 (59)	XLR	Dent Disease
HPRT1	Hypoxanthine	Davidson *AJHG* 48:951, 1991 (60)	XLR	Hyperuricemia
OCRL	Oculocerebrorenal syndrome of Lowe	Reilly *AJHG* 42:748, 1988 (61)	XLR	Dent Disease and Lowe Syndrome
PRPS1	Phosphoribosylpyrophosphate synthetase 1	Zikánová *Rheumatology* 57:1180, 2018 (62)	XLR	Phosphoribosyl Pyrophosphate Synthetase Superactivity
ADCY10	Soluble adenyly cyclase	Wang *AJTR* 12:4576, 2020 (63)	AD	Hypercalciuria
SLC25A25	Solute Carrier Family 25 Member 25	Jabalameli *Mol Genet Genomic Med* 9:1749, 2021 (64)	AD	Nephrolithiasis

AR, autosomal recessive; AD, autosomal dominant; DR, digenic recessive; XLR, X-linked recessive.

Clinical diagnosis of kidney stone disease

With the rising incidence of pediatric nephrolithiasis, it is crucial for healthcare providers to use optimal diagnosis strategies (66). Symptoms of nephrolithiasis may vary, or appear mild in pediatric populations, therefore a high index of clinical suspicion is warranted particularly in individuals with a positive family history of stone disease (67). Evaluation requires a complete medical history and physical examination, along with laboratory investigations and diagnostic imaging as outlined below (68). Although symptoms are variable, many patients will present with either renal colic (episodic pain in the renal angle) or hematuria associated with abdominal pain (66). After acute management of symptoms, diagnostic imaging is required to confirm the presence of one or more stones (66). This can include computed tomography (CT) scan, ultrasound or kidney and urinary tract, or X-ray film of the abdomen, all of which may help confirm the presence or absence of stone disease (66). Ultrasound is specifically recommended in pediatric populations, as opposed to the computed tomography scan used in adult populations, although it should be noted that ultrasound may have limitations in its capacity to detect stones (67–69). If stone presence is verified by imaging, a detailed family history and complete metabolic evaluation are warranted (66). A urology consult may also be necessary if the patient has renal colic, infection is present, the stone is larger than 5mm making spontaneous passage of the stone unlikely, or there are sign of obstruction within the urinary tract (66).

In pediatric patients, it is recommended that a complete in-depth metabolic analysis is completed (70). This consist of serum and 24-hour urine tests, as well as spot urine analysis and a full dietary history (70). A 24-hour urine collection collects

data on volume, creatinine, calcium, sodium, potassium, oxalate, citrate, uric acid, magnesium, and cystine (70). Analysis of blood samples should also be completed, and include serum sodium, potassium, bicarbonate, creatinine, calcium, phosphorus, magnesium, uric acid, citrate, parathyroid hormone (PTH) and vitamin D evaluation (66). These tests provide evidence of either the presence of promoter substances (i.e., excess calcium in the urine) or absence of inhibitor substance (i.e., low urinary citrate levels). These evaluations can provide evidence for underlying metabolic disorders such as hypercalciuria, hyperoxaluria, hyperuricuria, and hypocitraturia (68), all which can promote stone formation. The gold standard for confirming stone type is analysis of the stone composition following passage or extraction and recovered of a stone (66). If all tests are inconclusive, one may require genetic evaluation to determine disease causation.

Genetic evaluation in kidney stone disease

Currently, the Canadian Urological Association (CUA) Guidelines do not recommend genetic testing as a first tier diagnostic tool for pediatric patients with isolated kidney, however it is recommended as a future direction in patients with recurrent nephrolithiasis (70). Genetic testing was previously too costly and unavailable to many patients, but this has changed with new advancements in high throughput next sequencing techniques, allowing patients to receive genetic evaluations at ever reducing costs (13). In Canada, genetic testing is available with government funding through targeted gene panel sequencing, which may include a comprehensive gene panel. In many instances the comprehensive panel is denied funding, therefore whole exome sequencing (WES) is completed at the patient's expense, but more often through enrollment in a research project. There is mounting evidence that any child presenting with stone disease, particularly in the absence of obvious environmental precipitants, should undergo a full genetic workup as this is the only way to confirm a heritable nephrolithiasis disorders many of which pose a distinct risk for renal failure (71). It has been reported that of patients recruited from renal stones clinics, 14.9% had monogenic causation, and 40% had novel gene mutations associated with nephrolithiasis (72).

Next generation sequencing analysis in association with copy number variant analysis is currently the methods of evaluation of choice to identify a monogenic or single gene causes of kidney stone disease. Broadly, next generation sequencing in clinical practice methods include whole exome sequencing, whole genome sequencing (WGS) and targeted gene panel testing (73). WES is a method of determining the DNA sequence of the protein coding regions (exons) of the genes across the genome (74). WGS, on the other hand, sequences the genome in its entirety, including the protein coding regions (exons), non-coding regions (introns), as well as other non-genic portions of the genome (75). Both techniques facilitate the detection of variants in both known monogenic causes of kidney stone and both have the added advantage of allowing for novel gene detection (73). The use of WGS is increasing as it allows for evaluation for deep intronic variants and copy number variant analysis, both of which can be limited in standard exome analysis. Targeted gene panels increasingly is performed on an exome backbone but targets only specific gene know to be causative of the disease phenotype in question, therefore a high index of clinical suspicion for the underlying cause of disease is warranted pre-testing (76). The benefit of panel testing is that the data output is more simplified as analysis omit potentially less-relevant genes or regions of the genome thereby reducing the likelihood of detection of incidental findings (76). In recent years exome based analysis has largely replaced targeted gene panel tests, as it can detect the ever growing number of "new" kidney stone causing genes that are discovered across the genome (73). Figure 2 displays a potential diagnostic strategy for a pediatric nephrolithiasis population.

Treatment

Pediatric nephrolithiasis comes with a variety of symptoms, or can be asymptomatic, leading to different treatment approaches depending on initial symptoms (5). Some stones are passed spontaneously, though studies have not supported the hypothesis that spontaneous passage occurs at a higher rate in pediatric patients compared to adults (68). Acute management of pediatric nephrolithiasis upon diagnosis includes pain control, observation, medical expulsive therapy (MET), and surgical intervention (77, 78). MET is frequently employed among pediatric patients, and includes alpha-blockers or calcium channel-blockers due to the theorization that they relax the distal ureter, facilitating stone passage (77). A few studies have supported this hypothesis, further promoting the efficacy of MET over analgesics alone (79, 80). Surgical intervention has been reported to be required in 22-60% of pediatric patients (81). Options for such procedures include extracorporeal shockwave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL), retrograde intrarenal surgery (RIRS) with ureteroscopy (77). Pediatric nephrolithiasis cases specifically place patients in a high-risk category due to their high recurrence rates, significantly increasing the need for evaluation of risk factors (77). Metabolic abnormalities, anatomic abnormalities, as well as genetic conditions are among such factors (77). Ultimately, prevention of stone recurrence becomes the focus after acute management has been completed and depends on underlying causes of the formation of the stones. If metabolic conditions are known to underlie such cases, then dietary changes and pharmacological

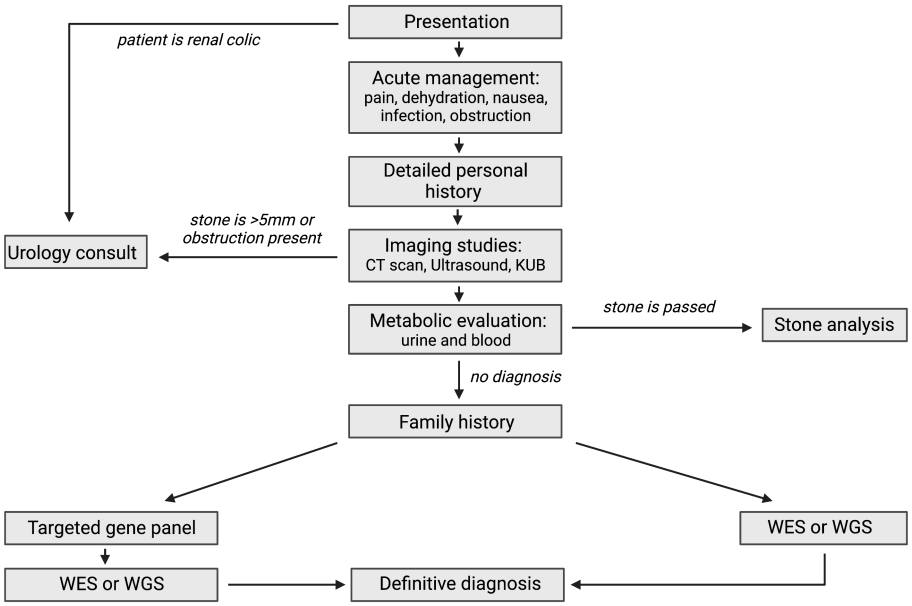

FIGURE 2
Complete overview of diagnostic methods for pediatric nephrolithiasis. KUB (kidney urinary bladder scan), WES (whole exome sequencing), WGS (whole genome sequencing). Created using BioRender.com (14).

intervention are performed (77). Nevertheless, adequate fluid intake remains pivotal in the attempt to prevent stone recurrence (68).

Genetic causes of kidney stone disease

Monogenic kidney stone disease demonstrates a Mendelian pattern with autosomal dominant, autosomal recessive and X-linked of inheritance reported. In many of the pediatric populations reported to date, pathogenic mutations were more likely detected in those with younger age of onset of disease (<10 years) with an autosomal recessive inheritance observed in the majority of cases (65).

Currently, there are 41 known genes with monogenic causation for nephrolithiasis (Table 1). Most of these genes encode renal solute transporters including Solute Carrier Family 12 Member 1 (*SLC12A1*), and Solute Carrier Family 34 Member 3 (*SLC34A3*), along with many others (82). These proteins are divided into families but are largely responsible for the transport of different solutes including glucose, heavy and light subunits of heterodimeric amino acids, bicarbonate, sodium, chloride cations, organic ions, anions, and phosphate in the kidney (82). Another group of causative genes include a genes that code for the chloride channel, voltage-sensitive 5 (*CLCN5*), which encodes for tight-junction proteins including Claudin 16 (*CLDN16*) and Claudin 19 (*CLDN19*). Metabolizing enzymes like such as Alanine-glyoxylate Aminotransferase (*AGXT*) and Cytochrome P450, family 24, subfamily A, polypeptide 1 (*CYP24A1*) (13) have also been implicated in disease. Of the 41 nephrolithiasis causing genes, 4-Hydroxy-2-Oxoglutarate Aldolase 1 (*HOGA1*), *AGXT*, and Solute Carrier Family 3 Member 1 (*SLC3A1*) are most commonly reported in pediatric patients with nephrolithiasis, followed by mutations to Solute Carrier Family 7 member 9 (*SLC7A9*) and Glyoxylate reductase/hydroxypyruvate (*GRHPR*) (65). Additionally, Solute Carrier Family 34 Member 1 (*SLC34A1*), ATPase, H+ Transporting, Lysosomal 56/58kDa, V1 Subunit B1 (*ATP6V1B1*), *CLCN5*, *CLDN16*, *AGXT* and *CYP24A1* are seen to cause early onset nephrolithiasis, all with an age of onset under 18 years (72). Many of these monogenic disease genes also contribute to individual monogenic forms of nephrolithiasis. Syndromic diseases including Bartter, Lowe, Dent, FHHNC and distal RTA have a recessive mode of inheritance, however heterozygous, dominant pathogenic mutations have been identified in individuals with milder clinical phenotypes (13). Here we will discuss individual monogenic forms of nephrolithiasis and nephrocalcinosis (Table 2).

Though many monogenic forms of nephrolithiasis follow Mendelian genetics, incomplete penetrance and variable expressivity have been well described, which may complicate genetic evaluation and pedigree analysis. Briefly, penetrance is the likelihood a clinical condition will occur when a genotype is present, and is described as incomplete when not all individuals with a given genotype (i.e. a certain mutation in a disease causing gene) develop the condition (83). Variable expressivity is the range

TABLE 2 Monogenic nephrolithiasis diseases. The table described the disorder, its OMIM number, gene, age of onset, clinical features, and stone type.

Disorder	OMIM#	Gene	Age onset	Clinical features	Type of stone
Dent Disease 1	300009	*CLCN5* Chloride channel, voltage-sensitive 5	< 10 years	*Growth:* short statue & poor growth *Kidneys:* proximal renal tubule defect, decreased renal tubular phosphate resorption, nephrocalcinosis, nephrolithiasis, renal failure in adulthood, renal insufficiency *Skeletal:* rickets, osteomalacia, increased fractures, bone pain, sparse bone trabeculae, thin bony cortex, limb abnormalities *Lab findings*: low-molecular-weight proteinuria, hypercalciuria, hypophosphatemia, hyperphosphaturia, aminoaciduria, glycosuria, microscopic hematuria, increased serum 1,25-dihydroxyvitamin D3	Calcium
Dent Disease 2	300555	*OCRL* Oculocer-ebreorenal syndrome of Lowe	< 10 years	*Growth*: short stature *Eyes*: mild ocular nuclear density *Abdomen*: umbilical hernia *Kidneys*: proximal tubule defect, nephrocalcinosis, renal insufficiency, nephrolithiasis *Neurologic*: developmental delay, cognitive impairment *Lab findings*: low-molecular-weight proteinuria, hypercalciuria, increased creatinine kinase, increased lactate dehydrogenase	Calcium
Lowe Syndrome	309000	*OCRL* Oculocer-ebrorenal syndrome of Lowe	< 1 year	*Growth*: short stature, failure to thrive *Eyes*: congenital cataract (males), glaucoma, microphthalmia, decreased visual acuity, corneal keloid, fine lens opacities, dense posterior cortical cataract *Teeth*: dental cysts, enamel hypoplasia *Gastrointestinal*: constipation *Genitourinary*: cryptorchidism (males), renal failure, nephrolithiasis *Skeletal*: joint hypermobility, osteomalacia, renal rickets, pathogenic fractures, scoliosis, kyphosis, platyspondyly, hip dislocation genu valgum, finer and wrist swelling, tenosynovitis, flexion and contractions of the digits *Skin*: sebaceous cysts, subcutaneous nodules *Neurologic*: neonatal hypotonia, areflexia, intellectual disability, seizures, ventriculomegaly, periventricular cysts, aggressiveness, tantrums *Metabolic features*: proximal renal tubular acidosis, Renal Fanconi Syndrome *Prenatal manifestations*: elevated amnionic fluid and maternal serum a-fetoprotein *Lab findings*: bicarbonaturia, aminoaciduria, proteinuria, phosphaturia, elevated serum acid phosphatase and protein, abnormal serum protein electrophoresis, elevated total cholesterol, deficiency of PtfIns (4, 5)P (2)5-phosphatase fibroblasts	Calcium oxalate and calcium phosphate
FHHNC	248250	*CLDN16* Claudin 16	2-5 years	*Growth*: failure to thrive *Eyes*: strabismus, nystagmus, hyperopia, myopia, astigmatism *Gastrointestinal*: abdominal pain, feeding problems *Genitourinary*: polyuria, nephrocalcinosis, progressive renal insufficiency, renal failure, nephrolithiasis, renal magnesium and calcium wasting, recurrent UTI *Muscles*: tetany *Neurologic*: seizures *Metabolic features*: polydipsia, incomplete distal renal tubular acidosis *Lab findings*: hypomagnesemia, normal serum calcium, elevated PTH, hyperuricemia, hypomagnesuria, hypercalciuria, hypocitraturia, hematuria, abacterial leukocyturia	Calcium
FHHNC with severe ocular involvement	248190	*CLDN19* Claudin 19	< 2 years	*Eyes*: myopia, nystagmus, strabismus, astigmatism, tapetoretinal degradation, macular coloboma *Teeth*: amelogenesis imperfecta, yellow-brownish discoloration, hypoplastic enamel, cusp malformation, diffuse opacities, hypomineralized linear demarcated opacities, hypoplastic grooves, areas of total enamel absence, microfractures *Genitourinary*: nephrolithiasis, nephrocalcinosis, progressive renal failure, real calcium and magnesium wasting, recurrent UTI *Lab findings*: hypomagnesemia, normal serum calcium, hypermagnesiuria, hypercacliuria	Calcium

(Continued)

TABLE 2 Continued

Disorder	OMIM#	Gene	Age onset	Clinical features	Type of stone
Distal RTA 1	179800	*SLC4A1* Solute Carrier Family 4 Member 1	Adolescence	*Kidney*: nephrolithiasis, nephrocalcinosis *Skeletal*: rickets, osteomalacia *Metabolic features*: primary distal renal tubular acidosis, hyperchloremic hypokalemic metabolic acidosis, secondary erythrocytosis *Lab findings*: hypokalemia, urine pH >6.4, hypercalciuria, hypocitraturia	Calcium phosphate
Distal RTA 2 with sensorineural hearing loss	267300	*ATP6V1B1* ATPase H+ transport-ing lysosomal 56/58kDa, V1 subunit B1	1-6 years	*Growth*: growth retardation, failure to thrive *Ears*: sensorineural hearing loss, severe-profound *Gastrointestinal*: feeding problems, vomiting *Kidneys*: nephrocalcinosis and nephrolithiasis *Skeletal*: rickets *Metabolic features*: primary distal renal tubular acidosis, hyperchloremic hypokalemic metabolic acidosis, dehydration	Calcium phosphate
Distal RTA 3 with or without sensorineural hearing loss	602722	*ATP6V0A4* ATPase H+ transport-ing lysosomal V0 subunit a4	1-4 years	*Ears*: normal hearing or sensorineural hearing loss mil-severe *Kidneys*: nephorcalcinosis and nephrolithiasis *Skeletal*: rickets *Metabolic features*: primary distal renal tubular acidosis, hyperchloremic hypokalemic metabolic acidosis *Lab findings*: hypokalemia, urine pH.6.5, hypercalciuria	Calcium phosphate
Distal RTA 4 with hemolytic anemia	611590	*SLC4A1* Solute Carrier Family 4 Member 1	Adolescence	*Growth*: height and weight less than 3rd percentile, failure to thrive *Abdomen*: hepatosplenomegaly, hepatosplenomegaly, anorexia *Kidneys*: nephrocalcinosis, distal renal tubular acidosis, isothenuria *Skeletal*: rachitic bone changes *Neurologic*: lethargy *Metabolic features*: hyperchloremic metabolic acidosis *Hematology*: hemolytic anemia, microcytosis, reticulocytosis *Lab findings*: hypokalemia	Calcium phosphate
Osteoporosis, autosomal recessive 3, with renal tubular acidosis	259730	*CA2* Carbonic anhydrase II	Early childhood	*Growth*: short stature, failure to thrive, postnatal growth retardation *Ears*: hearing loss *Teeth*: malocclusion, persistence of primary dentition, caries *Skeletal*: osteoporosis, recurrent fractures *Muscle*: weakness, hypotonia *Neurologic*: symmetrical cerebral calcifications, developmental delay, intellectual impairment, optic nerve pallor *Metabolic features*: mixed proximal and distal renal tubular acidosis, hyperchloremic hypokalemic metabolic acidosis *Hematology*: mild anemia *Lab findings*: carbonic anhydrase II deficiency, hypokalemia, urine pH >6.5	Calcium
HHRH	241530	*SLC34A3* Solute Carrier Family 34 Member 3	Infancy to early childhood	*Growth*: failure to thrive, poor growth, growth retardation *Abdomen*: increased intestinal absorption of phosphate and calcium *Kidneys*: renal phosphate wasting, decreased tubular maximal for phosphate reabsorption per glomerular filtration rate, calcium nephrolithiasis *Skeletal*: rib deformities, rickets, increased fractures, bone pain, sparse bone trabeculae, thin bony cortex, other limb and skull abnormalities *Muscle*: hypotonia, weakness, difficulty walking and standing *Lab findings*: hypophosphatemia, increased serum 1,25-dihydroxyvitamin D3, increased serum alkaline phosphatase, decreased or low-normal serum PTH, normal serum calcium, hypercalciuria	Calcium
FIH	143870	*ADCY10* Soluble Adenyly Cyclase	Early childhood	*Kidney*: calcium oxalate nephrolithiasis *Lab findings*: hypercalciuria, increased erythrocyte-membrane calcium-magnesium-ATPase, increased sodium-potassium pump activity	Calcium oxalate
FHH1	145980	*CASR* Calcium-sensing Receptor	Variable	*Pancreas*: pancreatitis *Kidney*: nephrolithiasis *Endocrine features*: parathyroid adenoma *Lab abnormalities*: hypocalciuria, hypercalciuria, hypercalcemia, hypermagnesemia, urinary calcium creatinine ration <0.01:1, normal concentration of PTH	Calcium
IIH Type 1	143880	*CYP24A1* Cytochro-me P450	20 days to 10 months	*Growth*: weight loss, failure to thrive *Gastrointestinal*: vomiting *Kidneys*: polyuria, nephrocalcinosis, nephrolithiasis	Calcium

(Continued)

TABLE 2 Continued

Disorder	OMIM#	Gene	Age onset	Clinical features	Type of stone
		Family 24 Subfamily A poly-peptide 1		*Muscle*: hypotonia *Neurologic*: lethargy *Metabolic abnormalities*: suppression of intact parathyroid hormone levels *Lab findings*: hypercalcemia, hypercalciuria, dehydration	
IIH Type 2	616963	*SLC34A1* Solute Carrier Family 34 Member 1	20 days to 10 months	*Growth*: failure to thrive *Kidneys*: polyuria, hypercalciuria, nephrocalcinosis, reduced tubular phosphate resorption, possible nephrolithiasis *Muscle*: muscular hypotonia *Metabolic features*: hypercalcemia, hyerpohosphatemia, elevated calcitriol *Endocrine features*: low PTH	Calcium
Bartter Syndrome Type 1	601678	*SLC12A1* Solute Carrier Family 12 Member 1	Antenatal	*Growth*: short stature, low birth weight, failure to thrive *Vascular*: low-to-normal blood pressure *Gastrointestinal*: constipation, vomiting, diarrhea *Kidneys*: renal salt wasting, renal potassium wasting, renal juxtaglomerular cell hypertrophy/hyperplasia, polyuria, nephrocalcinosis, nephrolithiasis *Skeletal*: osteopenia, chondrocalcinosis *Muscle*: weakness, cramps, tetany *Metabolic features*: hypokalemic metabolic alkalosis, dehydration, fever *Endocrine*: hyperactive renin-angiotensin system, increased plasma renin, increased plasma aldosterone, hyperparathyroidism *Prenatal*: fetal polyuria, polyhydramnios, increased chloride levels, premature *Lab findings*: hypokalemia, increased serum prostaglandin E2, hyperprostaglandinuria, hypercalciuria, hypercalcemia, occasional hypomagnesemia, hypochloremia, hyposthenuria, increased urinary potassium, increased urinary chloride	Calcium
Bartter Syndrome Type 2	241200	*KCNJ1* Potassium Inwardly-rectifying channel subfamily J Member 1	Antenatal	*Growth*: short stature, low birth weight, failure to thrive *Head*: large head, prominent forehead, triangular face, large pinnae, large eyes *Vascular*: low-to-normal blood pressure *Gastrointestinal*: constipation, vomiting, diarrhea *Kidneys*: renal salt wasting, renal potassium wasting, renal juxtaglomerular cell hypertrophy/hyperplasia, polyuria, nephrocalcinosis, nephrolithiasis *Skeletal*: osteopenia, chondrocalcinosis *Muscle*: weakness, cramps, tetany *Neurologic*: developmental delay, intellectual disability, seizures, paresthesias *Metabolic*: hypokalemic metabolic alkalosis, dehydration, fever, polydipsia *Endocrine*: hyperactive renin-angiotensin system, elevated plasma renin, elevated plasma aldosterone *Hematology*, platelet aggregation defect *Prenatal*: fetal polyuria, polyhydramnios, increased chloride levels, premature *Lab abnormalities*: hypokalemia, increased serum prostaglandin E2, hyperprostaglandinuria, hypercalciuria, occasional hypomagnesemia, hypochloremia, increased urinary potassium and chloride, hyposthenuria	Calcium
Bartter Syndrome Type 3	607364	*CLCNKB* Chloride Channel Voltage-sensitive Kb	Variable	*Eyes*: multifocal yellow-white geographic, solid, choroidal lesions along the retinal vascular arcades, echogenic placoid calcified lesions at level of the sclera and choroid, normal retina and retinal pigment epithelium overlaying lesions *Vascular*: low blood pressure *Kidneys*: renal salt wasting, renal potassium wasting, impaired reabsorption of chloride, polyuria, nephrolithiasis *Muscle*: generalized weakness *Metabolic features*: dehydration, hypokalemic metabolic alkalosis *Endocrine*: hyperactive renin-angiotensin system, elevated plasma renin, elevated plasma aldosterone *Lab findings*: hypokalemia, increased serum bicarbonate, increased urinary potassium and chloride, hypocalciuria or normocalciuria	Calcium
Hypocalcemia, autosomal dominant with Bartter Syndrome & ADH	601198	*CASR* Calcium-sensing Receptor	~ 4 years	*Growth*: short stature (rare) *Larynx*: laryngospasm (rare) *Kidneys*: hypercalciuria, nephrocalcinosis, nephrolithiasis, decreased renal function *Skeletal*: osteoarthritis, increased bone mineral density in lumbar spine *Muscle*: muscle cramp, carpopedal spasm, tetany	Calcium

(Continued)

TABLE 2 Continued

Disorder	OMIM#	Gene	Age onset	Clinical features	Type of stone
				Neurologic: seizures, paresthesias, calcification of the basal ganglia *Endocrine*: hypocalcemia, lower PTH concentration, elevated serum phosphate, hypomagnesemia, hypokalemia, hyperreninemia, hyperaldosteronemia	

FHHNC (Familial Hypomagnesaemia with Hypercalciuria and Nephrocalcinosis, RTA (Renal Tubular Acidosis), HHRH (Hereditary Hypophosphatemic Rickets with Hypercalciuria), FIH (Familial Idiopathic Hypercalciuria), FHH1 (Familial Hypocalciuric Hypercalcemia), IIH (Infantile Idiopathic Hypercalcemia), ADH (Autosomal Dominant Hypocalcemia).

of symptoms individuals with the same genotype can experience (83). These phenomena are almost exclusively observed in autosomal dominant disease, an example of which is observed in primary hyperoxaluria (PH) (83) and mutations in the gene Alanine-glyoxylate Aminotransferase (*AGXT*), which is responsible for Primary hyperoxaluria type 1 (PH1) (83). Another gene, 4-Hydroxy-2-Oxoglutarate Aldolase 1 (*HOGA1*), which causes Primary hyperoxaluria type 3 (PH3), has alleles that are either fully penetrant or incompletely penetrant with the more penetrant mutations having stronger phenotypic effects (83). Studies have shown that variants of Solute Carrier Family 25 Member 25 (*SLC25A25*), which again cause dominant nephrolithiasis, can display incomplete penetrance (64).

Allelism is another concept of genetic variation where the type of mutation in a particular gene can determine the severity of the disease phenotype. Missense mutations are those which result in a single base pair substitution causing one amino acid change; truncating mutations cause the loss of several amino acids due to early termination of the protein (84). In general missense "milder" mutations are thought to confer a milder phenotype compared to truncating "severe" mutations, which tend to result in a more severe disease spectrum (85). This phenomena has also been observed in monogenic stone disease (86). Examples include Oculocerebrorenal Syndrome of Lowe (*OCRL*) which causes Dent Disease or Lowe Syndrome, depending on the location of the mutation within the *OCRL* gene (Figure 3), and Calcium-sensing Receptor (*CASR*) which causes Hypocalcemia with Bartter Syndrome, Familial Hypocalciuric Hypercalcemia (FHH), or Autosomal Dominant Hypocalcemia (ADH1) (86). Allelism therefore leads to variation in the clinical phenotype even among individuals with pathogenic mutations in the same gene (87).

Dent disease

Dent disease is a familial renal tubular disorder with a X-linked recessive mode of inheritance (88). It is caused by mutations in the Chloride Channel, Voltage-Sensitive 5 (*CLCN5)*, or Oculocerenrorenal Syndrome of Lowe *(OCRL)* (phosphatidylinositol 4,5-polyphosphate-5-phosphatase) (88). First discovered by Dent and Friedman in 1964, the disease is classified as hypercalciuric rickets associated with renal tubular damage (89). The clinical manifestations of this disease include poor growth, proximal renal tubule defect, decreased renal tubular phosphate reabsorption, nephrocalcinosis, nephrolithiasis, rickets, osteomalacia, increased fractures, bone pain, lower limb deformities, low weight proteinuria, hypercalciuria, hypophosphatemia, hyperphosphaturia, aminoaciduria, glycosuria, and microscopic hematuria (89, 90). Symptoms generally arise in males before the age of 10, and by the age of 30, 30-50% of patients are diagnosed with ESKD (86). Genetic testing has an important role in confirming diagnosis, and to determine the specific gene that is mutated (88). Since Dent Disease is a congenital genetic disease, available treatment focuses on relieving symptoms including preventing nephrolithiasis, and reduction of hypercalciuria (88). Approximately 50-60% of patients with Dent Disease have *CLCN5* mutations, 15% have mutations to *OCRL* and the remaining 25% have possible defects in other genes (86). The majority of *CLCN5* mutations are nonsense resulting in an early stop codon and truncated protein leading to loss of chloride conductance (86). Mutations in *OCRL* mainly occur in the 5' region of the gene in exons 4 to 15 which is the phosphatase domain of the protein (86). Dent Disease is also considered to be a form of hereditary nephrocalcinosis (91). With the loss of renal chloride channel *CLNC5* in the proximal tubule, there is a decrease in chloride reabsorption and therefore a decrease in calcium reabsorption, as well as prevention of charge dissipation creating an acidic environment, both leading to the development of calcium kidney stones (Figure 4) (91, 92). Previous studies have found that approximately 30% of patients with Dent Disease caused by *CLCN5* mutations have nephrolithiasis, and this has an early age of onset with a mean of 23 (93). *OCRL* is involved in the trans-Golgi system, and in the processes of receptor endocytosis and recycling by proximal tubular cells (94). Wu et al. (2012) also described *OCRL* as an inhibitor of the Transient receptor potential vanilloid subfamily member 6 (TRPV6)calcium channel which could cause hypercalciuria and calcium nephrolithiasis due to increased calcium absorption (95).

Lowe syndrome

Lowe syndrome is a rare multisystem disorder with X-linked recessive inheritance, affecting the eyes, nervous

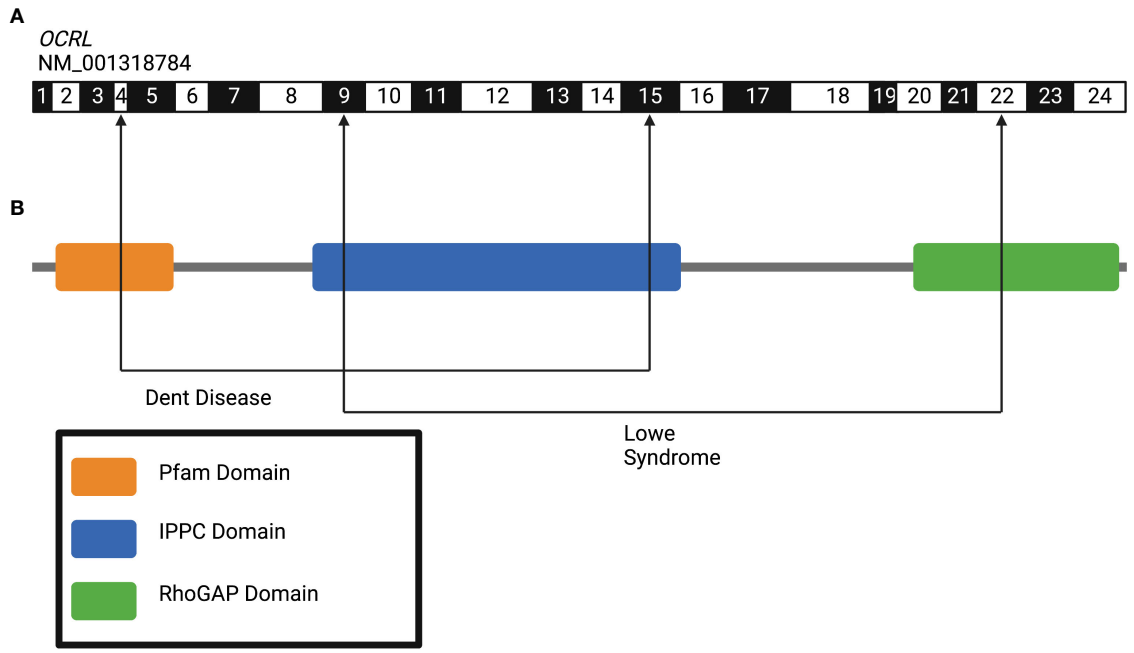

FIGURE 3
Allelism in the human gene Oculocerebrorenal Syndrome of Lowe (*OCRL*) gene leads to variation in clinical phenotypes of kidney disease. **(A)** Exon structure of human *OCRL* gene (NM_001318784) with arrowheads indicating exon positions wherein pathogenic variants lead to Dent disease (exons 4-15) and Lowe Syndrome (exon 9-22). **(B)** Protein domain structures of *OCRL* gene. Figure created using BioRender.com (14).

system, and kidneys (96). About 1 in 500,000 individuals suffer from Lowe Syndrome (96). This disorder is characterized clinically by symptoms including short stature, cataracts, glaucoma, renal failure, skeletal defects, osteomalacia, renal rickets, hypertonia, intellectual disability, seizures, Renal Fanconi syndrome, proximal renal tubular acidosis, bicarbonaturia, proteinuria, aminoaciduria, phosphaturia, elevated serum acid phosphatase, and elevated serum protein (97). In nearly half of nephrolithiasis cases, stones are composed of calcium oxalate and calcium phosphate (98). Most patients are in the pediatric population as Lowe Syndrome is a congenital genetic disorder (99). Life expectancy is no greater than 40 years, as the CKD is seen in the first year of life (stages 1 and 2) and progresses to stages 4 to 5 after age 20 (99). Treatment consists of removing cataracts, oral supplements of sodium and potassium bicarbonate or citrate to manage acidosis, oral supplementation of phosphate and calcitriol to manage hypophosphatemia and renal rickets, as well as growth hormones (100). The disorder is caused by mutations to the *OCRL* gene which encodes the protein phosphatidylinositol 4,5-polyphosphate-5-phosphatase (96). The *OCRL* gene on chromosome at position Xq26.1 when mutated causes a reduction in this protein and accumulation of the substrate phosphatidylinositol 4,5-polyphosphate (96). Affected patients have altered cell signaling pathways, defective actin cytoskeleton polymerization essential for formation of tight and adherens junctions in the renal proximal tubule, and protein trafficking abnormalities (96). Recent findings have also shown that *OCRL* is necessary for closure of endocytic vesicles which is important for recycling the megalin receptor in the proximal tubule (99). This defective recycling results in low molecular weight proteins in patients with Lowe syndrome (99). Due to allelism described above (Figure 3), pathogenic mutations in *OCRL* also cause Dent Disease. However, unlike Lowe Syndrome, patients do not have metabolic acidosis, ocular nor brain involvement (96). In patients with Lowe Syndrome, mutations to *OCRL* occur closer to the 3' end of the gene in exons 9 to 22 which encode large functional domains (86). This contrasts Dent Disease which, as previously mentioned, has most deleterious mutations at the 5' end of *OCRL* in exons 4 to 15 (86). Figure 3 depicts the *OCRL* exons and disease-causing regions. Due to the broad and variable symptoms of Lowe Syndrome, gene-targeted testing for *OCRL* (single-gene) or other potentially causative genes is important in providing a concrete diagnosis (100). Since this is an X-linked recessive disease, when a mother is a heterozygous carrier, there is a 25% chance of an affected son, and 25% chance of a heterozygous daughter (100). Some affected families may opt to do prenatal and preimplantation genetic testing, which is available once the familial *OCRL* pathogenic variant is detected (100).

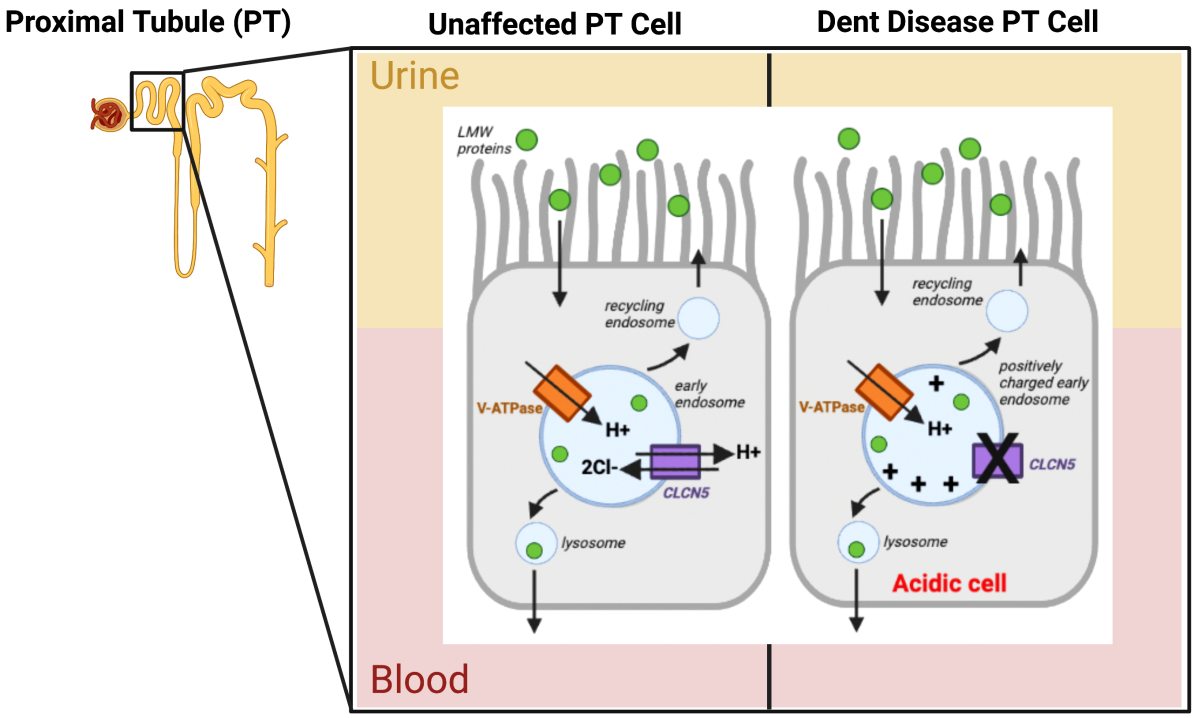

FIGURE 4
Pathophysiology of Dent Disease caused by Chloride channel, voltage-sensitive 5 (*CLC5*) mutation. The Vacuolar-type ATPase (V-ATPase) is represented by the orange rectangle, *CLC5* is depicted by the purple rectangle, with their arrows representing the flow of ions into/out of the early endosome. The green circles represent low molecular weight proteins (LMW proteins) with an arrow showing their flow into the cell. The X in *CLCN5* represents the dysfunctional protein, causing a charge build up in the early endosome and an overall acidic cell. PT cells are proximal tubule cells in the nephron of the kidney. Other arrows show the endosome cycle. Figure created using BioRender.com (14).

Familial hypomagnesaemia hypercalciuria and nephrocalcinosis

FHHNC is an autosomal recessive renal tubular disorder characterized mainly by excessive calcium and magnesium excretion, and has early onset (101). Additionally, patients with FHHNC suffer from polyuria, nephrocalcinosis, bilateral nephrocalcinosis, hypomagnesemia, hyperuricemia, hypermegnesiuria, hypercalciuria, hypocitraturia, hematuria, recurrent urinary tract infection, nephrolithiasis, progressive chronic renal failure, seizures, and issues with eyesight (101). Due to progressive loss of kidney function, 50% of patients require renal replacement therapy as early as age 20 years (102). As with other rare genetic disorders, there is no specific treatment for FHHNC, though patients are given oral magnesium supplementation and thiazide diuretics to help combat the progression of nephrolithiasis and nephrocalcinosis, though this does not protect renal function (101). FHHNC is caused by mutations to members of the claudin protein family, *CLDN16* and *CLDN19* (102). Claudin proteins are transmembrane proteins required for tight junction barrier formation in epithelia (102). Both *CLDN16* and *CLDN19* are necessary for the reabsorption of calcium and magnesium into the blood (103). When these proteins are dysfunctional, calcium and magnesium build up in the urine and cause nephrolithiasis and nephrocalcinosis (Figure 5) (103). *CLDN16* is located on chromosome 3q28 and is expressed exclusively in renal epithelial cells in the thick ascending limb of Henle and is important for reabsorption of divalent cations (104). Allelism has been in observed in patients with FHHNC. For example, a cohort of 69 patients with FHHNC due to pathogenic mutation to *CLDN16* showed that the age of onset for complete loss-of-function mutations is 2.2 years compared to mutations resulting in partial loss-of-function, which is 5.6 years (105). *CLDN19* is located on chromosome 1p34.2 and is expressed in the thick ascending limb of Henle as well as in the retinal pigment epithelium causing ocular defects in patients with *CLDN19* mutation distinguishing them from *CLDN16* patients (106). A study conducted by Val-Palomar found that in a Spanish cohort with 30 FHHNC patients who underwent exonic sequencing of *CLDN19* and *CLND16*, 90% of the patients analyzed had a mutation in *CLDN19* (106). Of the 90% with pathogenic *CLDN19* mutations, 74% had the homozygous glycine to aspartic acid change at amino acid position 20 mutation

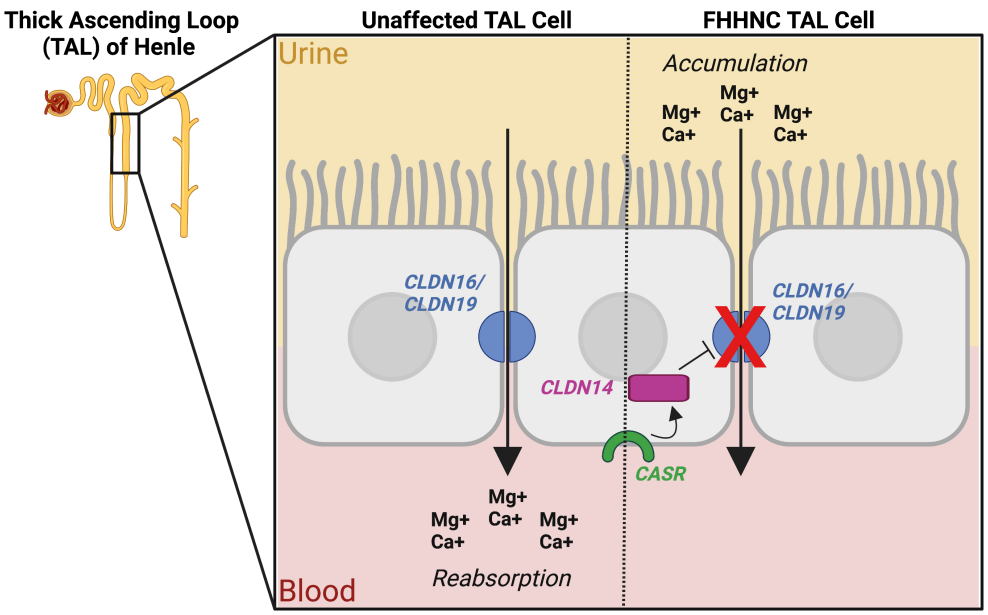

FIGURE 5
Pathophysiology of Familial Hypomagnesaemia Hypercalciuria and Nephrocalcinosis (FHHNC) caused by mutation in the genes Claudin 16 (*CLDN16)* and Claudin 19 (*CLDN19)*. The figure also shows the inhibiting role of calcium-sensing receptor (*CASR*) and Claudin 14 (*CLDN14*) on *CLDN16* and *CLDN 19* in some cases. The blue semi circles represent the tight junctions formed by the CLDN16 and CLND19 proteins, the green curve depicts *CASR*, and the magenta rectangle represents *CLDN14*. The arrows depict the flow of ions from the urine, through the tight junctions between cells, to the blood, and the red X depicts a dysfunctional, mutated *CLDN16* or *CLDN19*, preventing ion flow. TAL cell (Thick ascending loop of Henle cell, a cell found in the nephron of the kidney), Mg^{+} (Magnesium ion), Ca^{+} (Calcium ion). Figure created using BioRender.com (14).

(p.G20D) (106). This mutation is common in the South of Europe due to a common ancestor and has no change in CKD survival rate compared to patients with *CLND19* mutations (106). The mean age of onset of disease was 1.71 years (106). Nephrolithiasis has been reported in FHHNC patients with *CLDN16* and *CLDN19* mutations at a rate of 25% and 42% respectively (107). Variable expressivity has been described in families with FHHNC mutations; some present with isolated nephrolithiasis and/or hypercalciuria, but no other symptoms, suggesting that *CLDN16* may be associated with idiopathic calcium kidney stones (107). Recent research has also suggested *CLDN14* as a possible risk factor for the development of calcium-containing stone (108). *CLDN16* and *CLDN19* complex with Claudin 3, allowing for cation permeability in the thick ascending limb (TAL) tight junction of the loop of Henle (109). Claudin 14 (*CLDN14*) interacts with Claudin 16 (*CLDN16*) allowing calcium to flow through the junction, but mutations to *CLDN14* upregulate the protein and can cause nephrolithiasis (109). It has also been hypothesized that due to the interactions with *CLDN16* and the calcium-sensing receptor CASR, overexpression of *CLDN14* could cause hypomagnesemia, hypercalciuria and nephrocalcinosis as well, though this has not yet been related specifically to FHHNC (108).

Distal renal tubular acidosis

Distal RTA is an autosomal recessive or dominant kidney tubulopathy characterized by the inability to decrease urine pH to 5.3-5.5 when systemic metabolic acidosis is present (110). In this disease there is a defect in excreting H+ in the distal tubule and collecting duct of the nephron which leads to alkaline urine pH as well as calcium phosphate precipitation ultimately leading to kidney stones (111). General symptoms include nephrolithiasis, nephrocalcinosis, rickets, osteomalacia, primary distal renal tubular acidosis, hyperchloremic hypokalemic metabolic acidosis, urine pH>6.4 despite systemic acidosis, hypercalciuria, and hypocitraturia (110). Treatment of this disease includes alkali treatment which aims to correct metabolic acidosis and prevent rickets and stunted growth (112). There are three genes known to cause distal RTA including ATPase, H+ Transporting, Lysosomal V0 subunit A4 (*ATP6V0A4*), *ATP6V1B1*, and Solute Carrier Family 4, Anion Exchanger, Member 1 (*SLC4A1*) (110). *ATP6V0A4* and *ATP6V1B1* encode for different components of a multiunit V-ATPase enzyme that mediates acidification of eukaryotic intracellular compartments (110). In addition to the previously listed symptoms, individuals with a pathogenic or likely

pathogenic mutation in *ATP6V0A4* or *ATP6V1B1* may also suffer from mild to severe levels of sensorineural hearing loss, as well as a higher risk in developing nephrolithiasis and CKD (112). The average age of diagnosis for distal RTA caused by mutation to *ATP6V0A4* or *ATP6V1B1* is 5.5 years, as clinical manifestations normally begin at infancy (112). A member from the solute carrier family, *SLC4A1*, encodes for a protein expressed in the erythrocyte plasma membrane and in kidney cells and acts as a chloride/bicarbonate transporter for carbon dioxide transport from tissues to lungs, and in tubular acid excretion respectively (113). Some mutations to *SLC4A1* can therefore have pleiotropic effects in the kidney and red blood cells, which manifests as the autosomal recessive disease, distal RTA 4 with hemolytic anemia, while other mutations cause the autosomal dominant disease distal RTA 1 (113). For individuals with family history of pathogenic distal RTA mutations, prenatal genetic testing is available (114). Genetic testing to confirm the disease is also important since diagnosis can be challenging as it requires the physician's conjecture and measurement of urinary pH after an acid load, which would normally lower urine pH to 5.3 (111, 114).

Renal tubular acidosis with osteoporosis

RTA is caused by tubulopathy that creates alkaline urine due to the inability to lower urinary pH (110). Osteoporosis is a common disease with little known about pathogenesis, although data now shows that acid-base balance has a profound impact on the homeostasis of bone calcium, in the presence of a positive acid balance, alkali is released from the bone (115). This prolonged release of alkali from the bone causes increased bone resorption and a decrease in total bone substance, increasing the likelihood of developing osteoporosis (115). The clinical manifestations of this autosomal recessive disease are outlines in Table 2. RTA with Osteoporosis is caused by a mutation to the gene Carbonic Anhydrase II (*CA2*), which encodes a protein that catalyzes reversible hydration of carbon dioxide (116). *CA2* deficiency has also been determined to play a direct role in the loss of calcium from mineralized substrates and contributes to a rapid loss of bone mass, leading to osteoporosis (116). Both RTA type 1 (distal) and 2 (proximal) can lead to osteoporosis, though it is more common in type 2 (117). Osteoporosis is increasingly prevalent in the pediatric population due to increased disorders associated with bone loss including RTA with osteoporosis (118).

Hereditary hypophosphatemic rickets with hypercalciuria

HHRH is a rare autosomal recessive disorder caused by a defective sodium-phosphate co-transporter NPT2c due to loss-of-function mutations in the gene Solute Carrier Family 34 Member 3 *(SLC34A3)* (119). Pathogenic mutations in this gene are characterized by poor growth, renal phosphate wasting, decreased tubular maximum for phosphate reabsorption per glomerular filtration rate, calcium nephrolithiasis, rickets, increased fractures, bone pain, limb deformities, widened cranial sutures, muscle weakness, hypophosphatemia, increased serum 1,25-didroxyvitamin D3, increased serum alkaline phosphatase, decreased serum parathyroid hormone (PTH), and hypercalciuria (Figure 6) (119). The age of onset for HHRH is during infancy or early childhood. Treatment includes taking oral phosphate supplementation and potassium citrate, which can be enhanced by treatment with recombinant human growth hormone, fluconazole, and salt restriction (119). The solute transporter, *SLC34A3*, is expressed in proximal tubule cells of the kidney and transports phosphate into cells *via* sodium transport; its loss of function results in renal tubular defects (47). HHRH caused by mutations to both *SLC34A3* alleles (i.e. recessive disease) increase the risk of kidney stones to 46% compared to the general population risk of approximately 10% (120). It has been determined that heterozygous carriers of *SLC34A3* mutations can also develop isolated nephrolithiasis (120). Mutational screening for pathogenic variants in genes either through whole exome sequencing or gene panel testing is the method of choice to confirm the diagnosis (121). Genetic testing is also important in the family members since heterozygous mutations can also lead to stone disease, owing to the loss-of-function nature of *SLC34A3* (121).

Hypercalciuria

Hypercalciuria is a metabolic abnormality that causes excess calcium in the urine and is closely linked to causing calcium oxalate stones (122). There are many genetic disorders which are related to hypercalciuria and nephrolithiasis, including Dent Disease, FHHNC, HHRH, Autosomal Dominant Hypocalcemic Hypercalciuria (ADHH) and some forms of Bartter Syndrome, which are discussed in this review (122). Another form of hypercalciuria called Familial Idiopathic Hypercalciuria (FIH) is dominantly inherited and is caused by mutation to the gene, Soluble Adenyly Cyclase (*ADCY10*). The role of the ADCY10 protein is to catalyze the formation of the cAMP (123). FIH is common in children, and the main goal of treatment is to prevent recurrence of stones by reducing urinary calcium oxalate which can be accomplished by increasing fluid intake, low-salt diet, and some drugs including thiazides, diuretics, and potassium citrate (124). It has also been shown that in 69% of pediatric patients who suffered from nephrolithiasis and hypercalciuria there is a family history of the disorders (125).

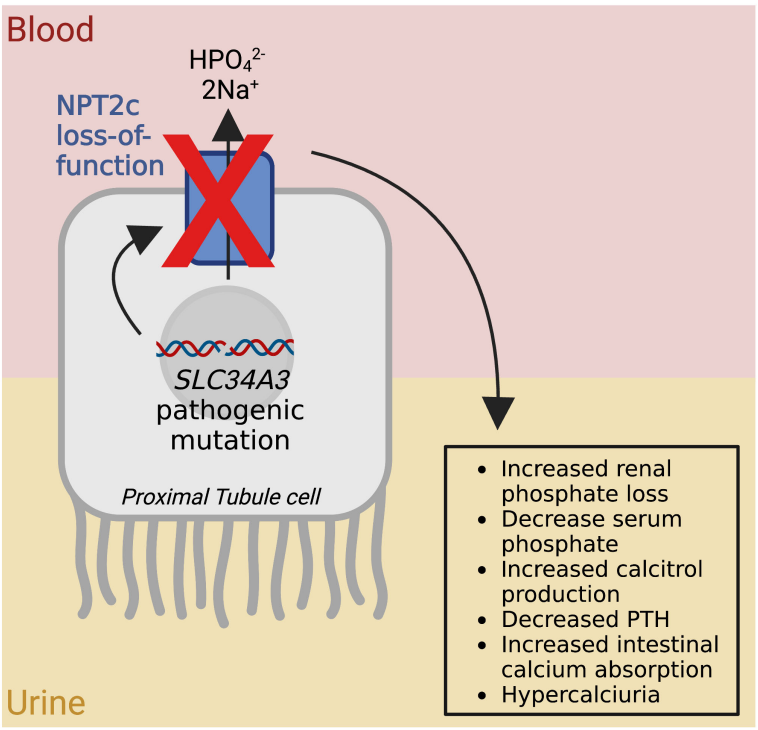

FIGURE 6
Pathophysiology of Hereditary Hypophosphatemic Rickets with Hypercalciuria. The red X represents the loss of function of the Type IIc Sodium-Dependent Phosphate Transporter (NPT2c) shown as a blue rectangle, due to a mutation to the Solute Carrier Family 34 Member 3 gene (*SLC34A3*). The arrow through NPT2c represents the flow of ions, and the other arrows show the flow from genotype to phenotype. HPO_4^{2-} (hydrogen phosphate), $2Na^+$ (2 sodium ions). Figure created using BioRender.com (14).

Hypercalcemia

Hypercalcemia occurs when calcium is two standard deviations above normal calcium levels over a period of three months (126). Genetic forms of hypercalcemia including Familial Hypocalciuric Hypercalcemia (FHH), and Infantile Idiopathic Hypercalcemia (IIH) (126).

FHH follows an autosomal dominant pattern with 65% of cases being caused by heterozygous inactivating mutations of the *CASR* on chromosome 3, and has variable age of onset (127). FHH is normally benign and asymptomatic, therefore diagnosis may be missed, or misdiagnosed as Primary Hyperparathyroidism which can result in unwarranted treatment or surgery if not correctly classified (127). Features of disease may include nephrolithiasis, pancreatitis, parathyroid adenoma, hypocalciuria, hypercalciuria, hypercalcemia, hypermagnesemia, and normal PTH (127). Most FHH cases do not require treatment, though calcimimetic drugs may be used if patients suffer from pancreatitis (127). Most cases of FHH that lead to death are due to improper and unnecessary treatment and surgery, which is why genetic testing for *CASR* is crucial (127).

Infantile Idiopathic Hypercalcemia (IIH) is an autosomal recessive disorder that is characterized by severe hypercalcemia (128). There are two types of IIH, type one is caused by mutation in the Cytochrome P450, Family 24, Subfamily A, Polypeptide 1 (*CYP24A1*), and type two is caused by mutations in the Solute Carrier Family 34 (*SLC34A1)* (128). General symptoms include failure to thrive, polyuria, nephrocalcinosis, hypotonia, hypercalciuria and hypercalcemia (128). Additionally, patients with Type 1 IIH may experience weight loss, vomiting, nephrolithiasis, central nervous system lethargy, and dehydration, whereas patients with Type 2 IIH may experience reduced tubular phosphate reabsorption, hypophosphatermia, elevated calcitriol, and low PTH (128). The age of onset for IIH is between 20 days and 10 months with failure to thrive and polyuria the most common presenting symptoms (128). There is strong evidence exhibiting nephrolithiasis in IIH Type 1 patients, though further research is needed to address the association of nephrolithiasis to IIH Type 2 (128).

Bartter syndrome

Bartter Syndrome is composed of a group of rare autosomal recessive genetic disorders causing defects in the kidney's ability to

reabsorb salt in the thick ascending loop of Henle (129). Bartter Syndrome is characterized by renal salt wasting, polyuria, hypokalemic metabolic alkalosis, elevated renin and aldosterone levels, and variable risk of developing kidney stones (129). There are 6 types of Bartter Syndrome with varying symptoms, and causative genes (129). Bartter Syndrome I (BARTS1) is antenatal in onset and is caused by mutation to the gene, *SLC12A1* (129). BARTS1 is a life-threatening form of the disease which presents with intrauterine growth retardation, premature delivery, low birth weight, failure to thrive, severe dehydration in the neonatal period, hypochloremia, hypercalciuria, hypercalcemia, increased urinary potassium and chloride, nephrocalcinosis, muscle weakness and cramping, as well as developmental delay (130). Currently, there are over 100 described mutations in the gene *SLC12A1* described in patients with BARTS1 (131). Bartter Syndrome II (BARTS2) is caused by mutations to Potassium Channel Inwardly Rectifying Subfamily J, Member 1 (*KCNJ1*), a gene that codes for the renal outer medullary potassium channel, ROMK, which controls resting potential, membrane excitability and is necessary for sodium chloride reabsorption in the ascending loop of Henle (132). Infants presenting with BARTS2 have polyhydramnios and premature delivery, failure to thrive, dehydration, nephrocalcinosis, muscle weakness, hypercalciuria, increased urine potassium and chloride, hyposthenuria, hyperprostaglandinuria, large head, prominent forehead, and large eyes, as well as neurological issues and muscle weakness and cramps (133). Studies have shown that 1 in 5 patients with BARTS2 also have nephrolithiasis (134). Although it is uncommon, there have been few cases reporting late-onset BARTS2 in adolescence and adulthood (132). Bartter Syndrome III (BARTS3) is caused by mutations to the kidney Chloride Channel, Voltage-sensitive Kb (*CLCNKB*), resulting in reduction of chloride and sodium reabsorption in renal tubules and subsequent loss of salt in urine (63). Additional symptoms of individuals with BARTS3 include low blood pressure, choroidal lesions and placoid calcified lesions to the eye, renal potassium wasting, impaired reabsorption of chloride, muscle weakness, dehydration, and increased serum bicarbonate, urinary potassium, and chloride (63). Pathogenic mutations in *CLCNKB* have also been proven to cause hypercalciuric nephrolithiasis (79). Previous work by Cheng et al. correlated severity of *CLCNKB* genotypes to age of onset, plasma chloride concentration, and urine excretion rate: milder missense mutations have a later age of onset (135), while truncating variants of *CLCNKB* cause a more severe, early onset BARTS3 phenotype (63). Bartter Syndrome IVA is caused by mutations to the gene Barttin CLCNK-type Accessory Subunit Beta, *BSND*. This disease normally develops in neonates during the second trimester (136). Infants with this disorder have additional symptoms including failure to thrive, sensorineural deafness, inability to concentrate urine, decreased glomerular filtration rate, renal failure, glomerulosclerosis, intellectual and motor disability, hyponatremia, hypochloremia, as well as increased urinary sodium, potassium, and chloride (136). Bartter Syndrome IVB is a digenic disorder caused by mutations to both kidney chloride channels, *CLCNKB* and Chloride Voltage-gated Channel Ka (*CLCNKA*) (129). Bartter Syndrome type 5 (BARTS5) is caused by X-linked recessive mutation of the gene Melanoma Antigen, Family D2 (*MAGED2*), and is a severe antenatal form of Bartter Syndrome (137). Almost all infants born with BARTS5 are premature, with 38% being born before gestational week 8 (137). These patients have a very high mortality rate and additional symptoms including severe renal sodium and chloride loss, hypercalciuria, nephrocalcinosis, preterm delivery, early onset severe polyhydramnios, hyponatremia hypochloremia, hyperreninemia, and elevated calcium to creatinine ratio (137). Prenatal genetic testing for *MAGED2* is important to prevent unnecessary diagnostic measures and harmful treatment in pregnant women (137). Studies have also classified an autosomal dominant form of BARTS5 as Hypocalcemia with Bartter Syndrome, which is caused by mutation to the gene *CASR*, and symptoms include kidney stones (129).

Hypocalcemia

Hypocalcemia is an electrolyte imbalance that can be potentially fatal, and in children, persistent hypocalcemia can be detrimental to bone growth and overall health (138). Patients with hypocalcemia have symptoms including short stature, laryngospasm, hypercalciuria, nephrocalcinosis, nephrolithiasis, decreased renal function, osteoarthritis, seizures, paresthesia, hypocalcemia, low PTH concentration, mildly elevated serum phosphate, hypomagnesemia, hypokalemia, hyperreninemia, and hyperaldosteronemia (139). Treatment for hypocalcemia aims to raise serum calcium to reduce symptoms therefore knowing the etiology of the disease is essential (139). Heterozygous mutations to the calcium-sensing receptor, *CASR*, cause genetic forms of hypocalemia (140). The protein encoded by *CASR* is a plasma membrane G-protein-coupled receptor that senses changes in circulating calcium concentration, coupling this information with parathyroid hormone regulatory pathways (140). A genetic form of hypocalcemia is ADHH (122). These patients have mild hypocalcemia that is generally asymptomatic but is can be associated with carpo-pedal spasm and seizures. The causative mutations is a gain of function mutation in the *CASR gene* (122), leading to hypercalciuria in these patients and subsequently nephrolithiasis (141). There are over 40 different *CASR* mutations, with many families having a unique deleterious mutation (122). Some forms of hypocalcemia do not have hypercalciuria, which is classified as Autosomal Dominant Hypocalcemia (ADH) (142). A study by Roszko showed that the 81% of patients were diagnosed with ADH1 before the age of 18, and the median age for diagnosis with hypocalcemia-related disorders is 4 years (141). These patients also have mutations to *CASR* which causes its activation and can lead to development of

ADH with BARTS5 (142). About 50% of patients with ADH have symptomatic hypocalcemia, and over 30% have intracerebral calcifications (142). Patients with ADH are treated with calcium supplements and active vitamin D metabolites to raise serum calcium, though this in itself can predispose patients to development of nephrolithiasis, as well as nephrocalcinosis and hypercalciuria (142). Genetic testing has an important place in diagnosis and treatment for the various types of hypocalcemia and should be performed along with genetic counselling for result interpretation and subsequent disclosures and explanations (141).

Conclusion

Nephrolithiasis is at an all-time high, with an increasing incidence in the pediatric population. Monogenic causation accounts for 30% of all nephrolithiasis cases, with a total of 41 known pathogenic genes. Mutations in a causative gene can lead to various monogenic nephrolithiasis disorders including Dent disease, Lowe Syndrome, FHHNC, RTA, RTA with osteoporosis, HHRH, hypercalciuria, hypercalcemia, Bartter Syndrome, and hypocalcemia. These diseases pose their own unique risks and symptoms associated with nephrolithiasis and diagnosis can be verified through genetic testing. There is a high inheritance correlation with a 3-fold increase in nephrolithiasis development in children with a family history. Nephrolithiasis may lead to CKD and ESKD, which is why precise diagnosis and treatment is vital. Current CUA guidelines do not recommend genetic testing as a first line diagnostic testing strategy for patients with isolated nephrolithiasis, though it is listed as a future direction to diagnose and treat genetic stones diseases (70). There is also increasing evidence that early diagnosis through genetic testing in the pediatric population may prevent the development of chronic kidney disease. Genetic testing options are now more available at ever reducing costs and include single gene testing, panel testing and large scale genomic testings such as exome or genome sequencing. With increasing available is it however imperative that all genetic testing and the subsequent interpretation of the results adheres to international guidelines. The American College of Medical Genetics and Genomics (ACMG) have published internationally accepted guidelines on how to determine whether a genetic finding is indeed disease causing. The ACMG recommend that all clinical molecular genetic tests fall into the pathogenic or likely pathogenic category (143). In addition, it is also recommended that all clinical molecular genetics results be reviewed and interpreted by a multidisciplinary team with an expertise in clinical genetics, and that pre- and post-counselling is provided to patients as necessary (143). With the growing numbers of novel genes and increased availability of genomic testing, both exome and genome sequencing is now proven techniques for detection of genetic kidney stones in pediatric populations and represents a future option for in the diagnosis and individualized treatment plans for children with suspected monogenic kidney stone disease.

Author contributions

CS conducted thorough literature review, developed Figures 1–6, edited Table 1, developed Table 2, wrote the drafts, carefully edited and revised various versions of the manuscript, collated all changes, added intellectual content, and approved the final manuscript. AP conducted thorough literature review, created Figure 3, aided in writing and editing the drafts, added intellectual content, approved the final manuscript. DMC conceived this project, added major intellectual input, provided Table 1, made multiple edits, approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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