# GENETICS OF MONOGENIC KIDNEY STONE DISEASE (KSD): A REVIEW

By

Mohammad Shoumik Saad Aarman

17136027

A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of Bachelor of Science in Biotechnology

Department of Mathematics & Natural Sciences

BRAC University

March, 2022

# DECLARATION

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

**Student's Full Name & Signature:**

Mohammad Shoumik Saad Aarman

Student ID: 17136027

# ACKNOWLEDGEMENT

First & foremost, all praise is due to Allah, Lord of the worlds, Who in His Infinite Knowledge, Wisdom & Mercy has granted this lowly servant of His the knowledge & ability to complete this work.

I express gratitude to Professor A F M Yusuf Haider, Chairperson of the Department of Mathematics & Natural Sciences at BRAC University, Dhaka, under whose authority I have pursued my Bachelors of Science in Biotechnology.

With deep gratitude and indebtedness, I acknowledge Dr. Iftekhar Bin Naser, Assistant Professor in the Department of Mathematics & Natural Sciences, for valuable suggestions and encouragement throughout this work.

Last but not the least, I remain indebted to my mother & then my father for all the love & kindness with which they have embraced & motivated me in my academic pursuits.

**Mohammad Shoumik Saad Aarman**

Student ID: 17136027

# ABSTRACT

Kidney stone disease (KSD) is a multifactorial illness characterized by a complex combination of hereditary and environmental variables. It generates enormous morbidity and medical care costs all over the globe. The majority of kidney stones are calcium-based, and they are frequently accompanied with a metabolic imbalance such as hypercalciuria. The effort to discover causal genes will offer a better knowledge of the pathophysiology of KSD. This will result in enhanced patient care quality and efficiency, as well as illness and complication detection, prevention, and control. This article reviews the understanding of documented monogenic KSD, as well as an update on molecular genetic investigations to examine genes responsible for the illness. Nephrolithiasis (kidney stone disease) is a prevalent issue that may be linked with changes in urine solute composition, including hypercalciuria. According to studies, approx. 15% of patients visiting kidney stone clinics had monogenic kidney stone illnesses such as renal tubular acidosis with deafness, Bartter syndrome, primary hyperoxaluria, and cystinuria. Genetic approaches to studying monogenic factors in nephrolithiasis have revealed that transporters and channels; ions, protons, and amino acids; the calcium-sensing receptor (a G protein-coupled receptor) signaling pathway; and the metabolic pathways for vitamin D, oxalate, cysteine, purines, and uric acid all play important roles in the aetiology of kidney stones. For NGS diagnoses of hereditary KSD, a complete gene panel is recommended. Accurate and timely diagnosis of hereditary forms of urolithiasis allows for the identification of a pathological germinal mutation and accurate diagnosis, analysis of heterozygous mutation carriage in affected families and evaluation of the prognosis of KSD development in family members, and personalized management of KSD patients.

# INTRODUCTION

Kidney stone disease (KSD) or nephrolithiasis is the creation of a hard mass inside the kidney, ureter, or bladder that contains protein and crystalline minerals. KSD patients have colicky flank pain, pain in abdomen, and painful urination, which is commonly accompanied by nausea, vomiting, hematuria, dysuria, and oliguria (Coe et al., 2005). KSD affects 5–15 percent of the global population, with a recurrence rate of 50% for up to 5–10 years and 75% within 20 years (Trinchieri et al., 1999; Moe, 2006). As a result, KSD is a significant clinical concern, resulting in medical care costs and a public health burden. KSD has a diverse aetiology, ranging from a flaw in a single gene to a complex combination of genetic and environmental variables (Coe et al., 2005). Occurrence of stone disease is relatively uncommon before age 20 but peaks in the $4^{th}$ or $6^{th}$ decade & vary with geography, climate, occupation, body mass index, weight, dietary habits & fluid intake. A higher prevalence of stone disease is found in hot, arid & dry climates such as mountains, deserts & tropical areas, but genetic factors & dietary influences may outweigh the effects of geography. Heat exposure & dehydration are high risk factors for stone disease aetiology. Stone disease may be caused by dehydration, vitamin A deficiency, infection, obstruction & prolonged immobilisation. But some factors like urinary citrate, magnesium, nephrocalcin, Tamm-Horsfall glycoprotein are potent inhibitors for urinary stone disease. With the invention of minimally invasive or non-invasive surgical techniques, management of renal stone disease has become easier, but due to high recurrence rate of urinary stone disease the patient & their family has been suffering physically & economically. For these reasons, researchers are very keen on unraveling the aetiology of urinary stone disease. Besides metabolic & non-metabolic causes, genetic correlations for stone disease recurrence is very important. Several scientific evidences have suggested that genetic factors play a role in the pathogenesis of

KSD, and a small number of monogenic forms have been identified, such as mutations in the calcium sensing receptor (*CASR*) gene in autosomal-dominant hypoparathyroidism and mutations in the claudin 16 (*CLDN16*) gene in familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (Attanasio, 2011; Vezzoli et al., 2011).

The understanding of the genetic effect on KSD has advanced dramatically during the last century. The discovery of the causal genes and detection of their variants has enabled molecular diagnostics, which has resulted in enhanced patient care quality and efficiency, as well as the identification of novel therapeutic targets and treatment modalities. In this review, I outline the genetic determinants of KSD and offer updates on molecular genetic research of the disease's genes in patients.

# NEPHROLITHIASIS MALADIES THAT ARE MONOGENIC

There are two types of nephrolithiasis disorders that are monogenic: those related with calcium-containing stones, which are radiopaque on plain abdomen X-ray, and those associated with stones that do not contain calcium and are either radiolucent or are radiopaque to a very low extent.

## Non-calcium nephrolithiasis maladies

Hereditary xanthinuria, cystinuria and adenine phosphoribosyltransferase (APRT) deficiency are all examples of non-calcium nephrolithiasis.

***Hereditary xanthinuria***

There are two clinically indistinguishable kinds of classical HX. Type I is characterized by a simple XDH/XO deficit caused by mutations in the XDH/XO gene on chromosome 2p23.1. Type II is characterized by a combined XDH/XO and aldehyde oxidase (AO) deficit caused by mutations in the molybdenum cofactor sulfurase gene (MOCOS), which is located on chromosome 18q12.2. Xanthine dehydrogenase/oxidase and AO are two enzymes that share a sulfurated MoCo & a common ancestor. HX type I seems to prevail based on the minimal data that exists. Because allopurinol is converted to oxypurinol by the action of XDH/XO and AO, oxypurinol is found in serum from HX type I patients owing to AO activity, but undetectable in HX type II patients due to combined XDH/XO and AO insufficiency. Molybdenum cofactor deficiency type A (OMIM 252150) is a third clinically separate entity defined by triple deficit of XDH, AO, and sulfite oxidase. This uncommon autosomal recessive illness is letgal & characterized by early onset in infancy and is caused by mutations in the MOCS1 gene (6p21.1). Intractable seizures, severe psychomotor reretardation and poor feeding with low serum and urinary uric acid and increased sulfite levels in urine are typically present.

The clinical repercussions of classical xanthinuria are related to xanthine's high insolubility in urine at any pH & increased xanthine removal by the kidneys. Unlike uric acid, the solubility of xanthine at pH 5.0 (0.5 mmol/L) is not significantly increased by urine alkalinisation (0.9 mmol/L at pH 7.0), posing therapeutic challenges. The high renal clearance of xanthine contributes to its potential toxicity in humans. As a result, the risk of precipitation in the kidney or urinary tract is considerable, especially in a newborn with a history of vomiting, diarrhea, or recurrent infection and may lead to tubular obstruction and acute renal failure. Renal injury has

resulted in clubbing of the calyces of the kidney, hydronephrosis, chronic renal failure, and nephrectomy in certain people. An adult patient with terminal uremia had plasma xanthine values of up to 243mol/L. HX can appear at any age, with children accounting for half of all reported cases. In 40% of patients, radiolucent xanthine stones & urolithiasis are present. Crystalluria, recurrent urinary tract infections, crystalluria, renal colic & hematuria are also non-specific features of HX. Irreversible kidney damage & acute kidney injury can result from xanthine stones if left undetected. Xanthine depositing in soft tissues over time in 10% of HX patients is responsible for duodenal ulcers, arthropathy & myopathy. Myopathy is the most common, with muscle pain and cramps being common symptoms that strenuous exercise frequently causes. In 20% of cases, HX is completely asymptomatic.

***Cystinuria***

With a median age of first stone of 26 years, SLC7A9 was by far the most frequent disease-causing gene in Halbritter et al.'s cohort. This conclusion is consistent with retrospective data acquired from stone composition analysis, which reveal cystinuria to be the most common monogenic cause of stone illness in adults. The presence of two pathogenic SLC7A9 mutations resulted in speedier manifestation in their cohort. Due to insufficient allelic segregation data, it was unable to determine whether the discovery of these mutations was due to recessive inheritance or the existence of two mutations on the same allele. Interestingly, clinical evidence in six people with mutant SLC7A9 did not raise the possibility of cystinuria, despite the fact that three of them had calcium-containing kidney stones. There have been new instances like these of calcium-based stones seen in people with heterozygous SLC7A9 mutations. Furthermore,

Martins et al. demonstrated that cystine enhances the production of calcium oxalate crystals in vitro, hinting that cystinuria may be a risk factor for calcium oxalate calculi. In conclusion, these findings highlight the need of screening urine for excess dibasic amino acids, particularly cystine, in all stone formers, even if the molecular genetic diagnosis has been confirmed. Although cystinuria is the most prevalent clinically recognized genetic diagnosis, only wide genetic screening revealed the etiology in some of these patients, impacting their future treatment and preventive actions that might subsequently be implemented.

Cystinuria (OMIM #220100) is a genetic disorder that affects, in the proximal tubules of the kidney, the transport of cystine, ornithine, lysine, and arginine (COLA)—the latter three are dibasic amino acids. Cystine, the least soluble of the four amino acids, can crystallize in the urinary tract, resulting in cystine stones. The COLA transporter ($b^{0,+}$) is a disulfide bridge-joined heterodimer of chromosome 2p16.3's *SLC3A1*-encoded rBAT and chromosome 19q13.1's *SLC7A9*-encoded $b^{0,+}$AT subunits.

Cystinuria genotypes are divided into Type A and Type B. *SLC3A1* mutations result in type A, *SLC7A9* mutations result in Type B. Clinical symptoms in the A and B subgroups are similar, and there is no obvious correlation between genotype and phenotype; however, relationships phenotype-genotype associations are being characterised. *SLC3A1* heterozygotes exhibit no phenotype, whereas SLC7A9 heterozygotes excrete variable levels of COLA in the urine. Stones will form in a small percentage of these patients, however the chances of this increases in case of low urine volume or high animal protein intake. now

***Adenine phosphoribosyltransferase deficiency***

APRT deficiency is caused by homozygous or compound heterozygous APRT mutations. Reduced APRT activity causes adenine accumulation, which is subsequently oxidized by XDH to produce 2,8-dihydroxyadenine; 2,8-dihydroxyadenine is extremely insoluble in urine, leading in crystalluria and radiolucent 2,8-dihydroxyadenine stone disease. Nephrolithiasis is the most common clinical sign of APRT deficiency. Furthermore, up to 20% of patients suffer with end-stage renal failure owing to tubulointerstitial damage from crystal deposition or obstruction, necessitating renal dialysis or transplantation. A kidney biopsy, the presence of 2,8-dihydroxyadenine crystals in urine, or the presence of decreased APRT activity in erythrocytes may all be utilized to establish a diagnosis. There are two types of APRT depending on whether there is a complete (type I) or partial (type II) APRT deficit in vitro; however, in vitro characterization of the mutant protein does not seem to alter the in vivo phenotype. Type II APRT has only been described among Japanese individuals.

A 540-bp coding region is found within *APRT,* which consists of 5 exons. 5-phosphoribosyl-1-pyrophosphate (PRPP) & adenine are the precursor, in a reaction involving $Mg^{2+}$ & catalysed by the APRT-encoded cytoplasmic homodimer enzyme APRT to 5'-adenosine monophosphate [Sahota et al 2001].

Silva et al 2004 discovered adenosine monophosphate (AMP)-bound recombinant human APRT's crystallised form. The protein, which has nine strands and six helices, is divided into three domains: a variable region largely engaged in base recognition, a flexible loop next to the core region that could contribute to catalysis, & a core area containing the PRPP-binding motif. The APRT gene, which is found on chromosome 16q24, has 2.8 kb of DNA, five exons, and a coding area of 540 bp. Individuals with APRT mutants on both chromosomes have complete APRT deficiency.

Mutant alleles responsible for type I have been labeled APRT*Q0, which refers to a heterogeneous collection of mutations scattered throughout the coding sequence, such as non-sense, deletion, missense & insertion mutations at the splice junction region, which results in aberrant mRNA splicing. For these variants, patients with type I deficiency have two of the mutated alleles, or the same allele, at the APRT locus. Some mutations seem to be more common in some groups. The IVS4+2insT mutation, which results in a shortened protein due to the intron 4 splice donor position having a thymine incorporated into it, accounted for 40% of the mutations in our sample. All probands with one copy of IVS4+2insT at the minimum were born in France or other European nations, but IVS4+2insT was not found in five other ethnic groups. The IVS4 +2insT mutation has already been reported in numerous European families and seems to be the most prevalent source of APRT deficiency in this community. Another prevalent mutation (Asp65Val), involving the substitution of one base with another, was discovered in patients from the United Kingdom, Iceland, and Spain. The Asp65Val mutation was confirmed to be homozygous in all 16 families studied in Iceland.

Type II APRT deficiency is caused by APRT*J, a base substitution restricted to exon 5 that places threonine instead of methionine at the 136$^{th}$ position of APRT's amino acid chain; it has only been documented in the Japanese population. Type II deficient patients are homozygous for the aforementioned allele; less often, they have one APRT*J allele & one APRT*Q0 allele. A missense mutation (V150F) described in a patient of Polish heritage resulted in an enzyme completely devoid of catalytic properties within their body; the enzyme was shown to have catalytic properties in vitro, however. This finding shows type II deficiency as being uncommon in non-Japanese people.

## Calcium nephrolithiasis maladies

Primary hyperoxaluria, Barterr syndrome, distal renal tubular acidosis & Dent disease are all calcium nephrolithiasis maladies.

### *Primary hyperoxaluria*

Primary hyperoxaluria is caused by hepatic amino acid metabolism abnormalities at AGXT, GRHPR, and HOGA1, which result in PH types 1, 2, and 3, respectively. This malady may manifest as infantile end-stage kidney disease, childhood or adult nephrocalcinosis with recurrent nephrolithiasis or infrequent stone production, or it can be unexpressed clinically. Patients who are affected are susceptible to the formation of calcium oxalate monohydrate stones. PH types 2 and 3 have lower urine oxalate excretion, which correlates with a much better prognosis. If urinary oxalate excretion surpasses 70 to 80 mg per day, PH should be regarded as responsible. Treatment requires genotyping since PH type 1 caused by AGXT Gly170Arg and Phe152Ile mutations responds to pyridoxine medication. Testing patients' response to pyridoxine therapy may be helpful for additional mutations.

200+ pathogenic or possibly pathogenic variants in the AGXT gene (NM 000030, located on 2q37.3), which encodes alanine:glyoxylate aminotransferase (AGT), have been determined until now. The gene at various positions contains splice junction loss (11%), start loss (1%), nonsense (13%), frameshifts (16%), inframe indel (3%) mutations, but the majority are missense mutations (54%). These modifications may have functional effects such as mistargeting of AGT to mitochondria rather than peroxisomes, disappearance of AGT immunoreactive & catalytic properties, and preservation of AGT immunoreactive properties with disappearance of catalytic properties.

Based on nucleotide substitutions at positions 32 and 1020 on the cDNA, two major polymorphic variants in the AGXT gene have been found. The minor allele is distinguished from the main (wild type) allele by Leu substituting Pro due to T substituting C at the $11^{th}$ & $32^{nd}$ positions of the amino acid chain & coding DNA strand, respectively; Met substituting Ile due to G substituting A at the $340^{th}$ & 1020nd positions of the amino acid chain & coding DNA strand, respectively, and a 74-bp insertion in intron 1. The p.Pro11Leu variation interacts with certain pathogenic variants by uncovering a mitochondrial targeting region which the region targeting the protein to peroxisomes competes with, resulting in mitochondrial AGT targeting that is reliant on the rate at which protein folding and dimerization occurs. The majority of mutations only occur in certain families, but others are more common. The pathogenic mutation p.Gly170Arg wrongly targets AGT to mitochondria and explains approxiamtely 30% of mutant alleles. The p.Ile244Thr variation, which is present in around 9% of all PH1 patients, is substantially more common with sufferers having North African heritage, with rates as high as 84 percent in Moroccan patients and 92 percent in Canaries individuals. Around 33.3% of PH1 sufferes respond to pyridoxine, a precursor of PLP, the AGT coenzyme, at therapeutic levels. Pyridoxine has been demonstrated in vitro to operate as a chemical chaperone, cause AGT to dimerise, strengthens the protein's 3D structure, and boost peroxisome targeting. Moreover, it acts as a prosthetic group, besides potentially boosting the catalytic activity of enzymes. The p.Gly170Arg and p.Phe152Ile missense pathogenic variants have been reported to be B6 responsive in individuals with PH1, with a considerable decrease in oxalate excretion (>30% reduction to complete normalization) and clinical improvement. Some case reports indicate patients with AGT in which Thr replaces Ile & Arg replaces Gly at the $244^{th}$ & $41^{st}$ positions of the amino acid chain, respectively, exhibit limited pyridoxine responsiveness.

Discrepancies in results from the observation & treatment of actual patients rather than theoretical or laboratory studies, particularly the beginning of ESRD, are impacted by genotype, highlighting the necessity of AGXT molecular investigation. Substitution of Gly with Arg at the $170^{th}$ position of AGT's amino acid chain in a number of cohort studies was linked with a better outcome, defined as delayed development to ESRD, when present in the homozygous condition. Null mutations, on the other hand, are often linked with a bad prognosis. The high inter-individual and intra-familial variation of the disease's clinical history shows that genes which modify the phenotypic expression of genes at other loci. The potential development of ESRD throughout childhood in null mutation-bearing children, but other patients get ESRD in infancy, demonstrates how little is known about PH. Even if metabolic studies are normal after ruling out conventional reasons for secondary hyperoxaluria, the conclusive diagnosis of PH1 needs AGXT genetic testing. The presence of pathogenic or likely pathogenic mutations in two alleles of the AGXT gene verifies the diagnosis. The use of massive parallel sequencing enhanced PH diagnosis by permitting the simultaneous investigation of AGXT and the genes implicated in PH2 and PH3. It is critical to ensure that the technology utilized can identify substantial copying &/or removal of base(s). Parental testing is required to confirm the bi-allelic segregation of the variations found in an index case and is required in cases when testing before birth or the attachment of the fertilized egg or blastocyst to the wall of the uterus at the start of pregnancy is required. Because the observable characteristics of an individual resulting from the interaction of their genotype with the environment show heterogeneity among families, it is advised to extend mutation analysis to siblings.

Studies with $^{14}C$-glycolate showed that glycolate was a major precursor to oxalate in PH1, and the concept of glycolate playing an important role in PH1 has been reinforced by normalization

of urinary oxalate in the double *Agxt Go* KO mouse, inhibition of GO by RNA interference, and CRISPR/Cas9 (a mechanism to modify cells' genetic material using clustered regularly interspaced short palindromic repeats/CRISPR-associated (Cas) 9). Clinical experiments employing GO-binding small interfering RNA (siRNA) recently revealed near-normalization of urinary oxalate in PH1, confirming the crucial involvement of AGT in detoxifying the glyoxylate generated by glycolate oxidation.

***Bartter syndrome***

The renal tubulopathy Bartter syndrome is caused by a deficiency in sodium chloride reabsorption in the loop of Henle. Hypokalaemic alkalosis, hypotension, hyper-reninaemic hyperaldosteronism, increased urine prostaglandin excretion, and hypercalciuria with nephrocalcinosis are all symptoms. So far, mutations in six genes have been linked to this feature. Mutations in the gene encoding the bumetanide-sensitive sodium potassium–chloride cotransporter (NKCC2; also known as SLC12A1) cause type I Bartter syndrome; mutations in the gene encoding the renal outer-medullary potassium channel (ROMK; also known as KCNJ1) cause type II; mutations in the gene encoding the voltage-gated chloride channel ClC-Kb (CLCNKB) cause type III; mutations in the gene Types I–IV are autosomal recessive, with type IV being associated with deafness owing to the expression of Barttin, a -subunit required for the trafficking of CLC-Kb and CLC-Ka in the potassium secreting marginal cells of the inner ear's scala medium. Type V Bartter syndrome is inherited autosomally and is characterized by heterozygous activating CASR mutations with a much lower EC50 than those seen in ADH patients; it is probable that the severity of CASR gain-of-function mutations influences the

clinical characteristics of Bartter syndrome. CLCN5 mutations are more often connected with Dent disease than with Type VI Bartter syndrome, which is transmitted as an X-linked recessive condition. NSAIDs inhibit renal prostaglandin formation, but spironolactone, which inhibits distal tubular sodium–potassium exchange, helps cure hypokalaemic metabolic alkalosis. Electrolytes should be replaced on a regular basis.

***Distal renal tubular acidosis***

Lightwood published the first description of type I distal renal tubular acidosis (dRTA) in an autopsy series involving six children in 1935. Albright and colleagues identified the tubular origin of the condition in 1946, and Pines and Mudge created the name "renal tubular acidosis" in 1951. Type I dRTA may be inherited or acquired. Type I dRTA may be caused by a variety of acquired reasons, the most common of which is Sjögren's syndrome, which is caused by autoantibodies aimed towards α–intercalated cells. The underlying monogenic causes of familial cases have been identified as autosomal-recessive and autosomal-dominant mutations in the anion exchanger 1 (AE1, encoded by the SLC4A1 gene), autosomal-recessive mutations in the B1 and a4 subunits of the V-ATPase (encoded by the ATP6V1B1 and ATP6V0A4 genes, respectively), and recently autosomal-recessive mutations in the transcription factor Foxi1 (encoded by the FOXI1 gene). Overall, type I dRTA is regarded as an uncommon cause of calcareous nephrolithiasis. Reduced urine net acid excretion and alkaline urinary pH are caused by rate- (or capacity-) constrained distal tubular H+ secretion. Unlike in pRTA, individuals with type I dRTA have systemic H+ retention. As a result of H+ retention, intestinal calcium absorption and calcium release from bone increase, but renal calcium reabsorption decreases,

leading to hypercalciuria. Another feature of type I dRTA is hypocitraturia caused by avid citrate reclamation by proximal tubular cells in the presence of systemic acidosis.

***Dent disease***

Dent's disease is caused by inactivating mutations in either the CLCN5 (OMIM #300008) gene that gives rise to ClC-5, a Cl-/H+ exchanger that is electrogenic, consists of 746 amino acids & is found within chromosome Xp11.2, or the OCRL1 gene, that gives rise to OCRL1 (phosphatidylinositol 4,5-biphosphate 5-phosphatase) that is found within chromosome Xq25. ClC-5 has 18 α-helices, two phosphorylation sites, and one N-glycosylation site. The protein generates diamond-shaped homodimers made of two repeating halves that cross the membrane in opposing orientations, according to structural investigations. One pore that is in charge of selectively connecting the Cl- flow to the H+ counter-transport is found in every subunit. There have been 148 documented *CLCN5* mutations, which are spread across the coding area with no indication of large mutational hot spots. Furthermore, no association seems to exist between mutations and phenotypes, neither does the set of observable characteristics of Dent's disease in an individual resulting from the interaction of the environment with the existence or non-existence of *CLCN5* having altered base sequences. Of the 148 *CLCN5* mutations identified, in every hundred mutants, around 3 are donor splice site mutants, 1 is a novel splice site mutant, 5 are changes in the ribosomal reading frame due to new base(s) being added, 33 involve replacement of a single base with another, 14 are changes in the ribosomal reading frame due to base(s) being removed, 1 is a removal of base(s) in the ribosomal reading frame, 36 involve the existence of a premature stop codon within the base sequence, 3 are acceptor splice site mutants,

1 is a full gene removal, 1 is an addition of base(s) in the ribosomal reading frame, & 2 are removal of base(s) within *CLCN5*. The majority are thought to result in shortened or missing ClC-5 protein, resulting in total antiporter function loss. Indeed, heterologous production of these *CLCN5* mutants from Dent's disease from HEK293 cells & also from oocytes of *Xenopus laevis* demonstrated that the majority of *CLCN5* mutations result in a loss of Cl-conductance. Further research into *CLCN5* missense mutations has found that they may cause one of three abnormalities: dispersal of ClC-5 within endosomes being changed without deficient endosomal acidification, faulty lowering of pH within endosomes, or ClC-5 being retained within the endoplasmic reticulum for subsequent destruction. The bulk of the missense mutations are concentrated within the regions where the subunits interact with each other, underlining the functional significance of ClC-5 homodimerisation. Furthermore, inactivating the *Clcn5* gene genetically in mice replicates the nephrocalcinosis, hypercalciuria & other such severe impairments in proximal tubules that constitute Dent's disease.

About 40% of people with Dent’s illness do not have *CLCN5* mutations, although their observable & recognisable symptoms can’t be differentiated from those without such mutations. Twenty of these individuals were discovered to have *OCRL1* mutations, albeit it is crucial to emphasize that none of them had disabilities in the faculty of reasoning and understanding objectively, especially with regard to abstract matters, or serious cataracts, that is characteristic of Lowe syndrome patients. Consistent with these clinical distinctions, there are *OCRL1* mutations linked to Lowe syndrome but not Dent’s disease, & vice versa. The *OCRL1* missense mutations that cause Dent’s disease results in aberrations in the OCRL1 domain with phosphatidylinositol phosphate 5-phosphatase activity that has its last base in exon 15 & first in exon 4, all within the segment including the 5’-end of the gene, while the truncating mutations

occur in the first seven exons or intron 7. In contrast, aberrations in the three big functional domains of OCRL1 in Lowe syndrome patients are mostly due to *OCRL1* mutations found within the region of the gene stretching from exon 22 downstream to exon 9 upstream. To explain the milder clinical traits reported in the former patients, there exists the hypothesis that in Lowe syndrome a decreased but functional OCRL1 version or isoform is absent, but it is present in Dent's disease 2. Thus, Dent's disease has genetic heterogeneity, with altered *CLCN5* base sequences in around 50-60 sufferers per 100 people (Dent disease 1), 15% having *OCRL1* mutations (Dent disease 2), and the other 25-35 percent having neither *CLCN5* nor *OCRL1* mutations but maybe problems in other genes. The idea that these additional genes encode some of the proteins that interact with ClC-5 (e.g., ClC-4 and cofilin) has been studied, without the discovery of altered *CLCN5* or *COFILIN* base sequences.

# CONCLUSION

Incidence of nephrolithiasis is rising continuously due to complex aetiological factors including a monogenic aspect. Multiple studies of monogenic disorders of nephrolithiasis have increased today's understanding of the transporters, channels & receptors involved in regulation of the renal tubular fluid composition which contributes to the risk of renal stone formation. Correct diagnosis of aetiological factors will help to prevent recurrence & will guide the management & enable screening for disease phenotypes & facilitate genetic counselling. Furthermore with the rapid advances in genomic medicine, we can hope individual drug therapy might become available based on genotype in individuals who are currently considered recurrent idiopathic kidney stone formers. Reviewing all these papers of multiple researchers, these precision

medicine approaches might become a reality & continued genetic studies may open up new pathways for understanding the causative factors & prevention of renal stone disease.

# REFERENCES

Bollée, G., Harambat, J., Bensman, A., Knebelmann, B., Daudon, M., & Ceballos-Picot, I. (2012). Adenine Phosphoribosyltransferase Deficiency. *Clinical Journal of the American Society of Nephrology* : *CJASN*, *7*(9), 1521–1527. https://doi.org/10.2215/CJN.02320312

Devuyst, O., & Thakker, R. V. (2010). Dent's disease. *Orphanet Journal of Rare Diseases*, 5, 28. https://doi.org/10.1186/1750-1172-5-28

Fargue, S., & Acquaviva Bourdain, C. (2022). Primary hyperoxaluria type 1: pathophysiology and genetics. *Clinical Kidney Journal*, *15*(Suppl 1), i4–i8. https://doi.org/10.1093/ckj/sfab217

Fuster, D. G., & Moe, O. W. (2018). Incomplete Distal Renal Tubular Acidosis and Kidney Stones. *Advances in Chronic Kidney Disease*, *25*(4), 366–374. https://doi.org/10.1053/j.ackd.2018.05.007

Halbritter, J., Baum, M., Hynes, A. M., Rice, S. J., Thwaites, D. T., Gucev, Z. S., Fisher, B., Spaneas, L., Porath, J. D., Braun, D. A., Wassner, A. J., Nelson, C. P., Tasic, V., Sayer, J. A., & Hildebrandt, F. (2015). Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. *Journal of the American Society of Nephrology : JASN*, *26*(3), 543–551. https://doi.org/10.1681/ASN.2014040388

Howles, S. A., & Thakker, R. V. (2020). Genetics of kidney stone disease. *Nature reviews. Urology*, *17*(7), 407–421. https://doi.org/10.1038/s41585-020-0332-x

Mraz, M., Hurba, O., Bartl, J., Dolezel, Z., Marinaki, A., Fairbanks, L., & Stiburkova, B. (2015). Modern diagnostic approach to hereditary xanthinuria. *Urolithiasis*, *43*(1), 61–67. https://doi.org/10.1007/s00240-014-0734-4

Policastro, L. J., Saggi, S. J., Goldfarb, D. S., & Weiss, J. P. (2018). Personalized Intervention in Monogenic Stone Formers. *The Journal of Urology*, *199*(3), 623–632. https://doi.org/10.1016/j.juro.2017.09.143

Sahota, A., Tischfield, J. A., Goldfarb, D. S., Ward, M. D., & Hu, L. (2019). Cystinuria: genetic aspects, mouse models, and a new approach to therapy. *Urolithiasis*, 47(1), 57–66. https://doi.org/10.1007/s00240-018-1101-7

Simmonds, H.A., Reiter, S. & Nishino, T. (1995). Hereditary xanthinuria. *The Metabolic and Molecular Bases of Inherited Disease*. 1781-1797.