

# Nephrolithiasis is caused by genetic abnormalities

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## ABSTRACT

The solubility of chemicals in the urinary system is affected by risk factors, which are frequently linked to the prevalence of renal stones. Although primary, or hereditary, reasons are uncommon, it is crucial to identify them in order to initiate the proper treatments and acknowledge the hazards to other family members.

The research of renal stones from a biochemical standpoint is briefly summarized, with an emphasis on potential issues. The disorders of

Adenine Phosphoribosyl Transferase (APRT) deficiency, primary hyperoxaluria, cystinuria, and autosomal dominant distal renal tubular acidosis are used to describe the genetic basis of renal stone disease caused by (i) Derangement of a metabolic pathway, (ii) Diversion to an insoluble product, (iii) Failure of transport, and (iv) Renal tubular acidosis.

**Keywords:** Genetics stones; Hyperoxaluria cystinuria; Distal renal tubular acidosis; APRT deficiency

## INTRODUCTION

Nephrolithiasis, often known as renal stones, is a prevalent condition

that affects anywhere between 6 and 15% of people in the western world. Most often, these are related to environmental risk factors, such as occupation, nutrition, inadequate fluid intake, absence of stone inhibitors, administration of insoluble medicines, such as antiretrovirals, or acquired diseases like hyperparathyroidism or anatomical abnormalities, such as the horseshoe kidney. A related condition called nephrocalcinosis may also point to calcium precipitation in the kidney [1].

A related condition called nephrocalcinosis may also point to calcium precipitation in the kidney. Nephrocalcinosis and nephrolithiasis are caused by inherited diseases, autosomal dominant, recessive, or X-linked disorders in a small but significant percentage of cases, and their diagnosis has implications for the disease's prognosis, treatment, and hazards to other family members. This review will concentrate on inherited kidney stone diseases. The article will concentrate on some fairly well defined metabolic causes, such as (i) Derangement of a metabolic pathway, (ii) Diversion to an insoluble product, (iii) Failure of transport, and (iv) Renal tubular acidosis. It is not intended to be completely inclusive because this would be impossible with an ever expanding list of disorders [2].

Any of the following renal stone disease risk factors, such as early age of onset, recurrent stones, bilateral stone disease, family history, or history of consanguinity, should raise suspicion of an inherited etiology [3].

Most clinical biochemistry laboratories have the ability to support early investigations either internally (for the bulk of tests) or by referring patients to specialty facilities (oxalate, citrate, cystine, primary hyperoxaluria metabolites). The analysis of the kidney stone, if it is available, can be helpful, but data from a third party quality assurance program managed by my lab suggests that not all laboratories offer a reliable service in this area, frequently misidentifying the types of stones, failing to identify other, more uncommon stone types, and giving no indication of the relative contribution of the various components. Physical analysis based tests, including infrared ones, are more likely to produce accurate results [4].

Through radiographic investigation, it will be possible to determine if *in-situ* stones are cysteine containing (faintly radio dense), calcium containing (radio-opaque), radiolucent (pointing to uric acid or other purine material), or both. Children with stone illness are more likely to have their metabolic

profiles analyzed than adults, who may only receive physical treatment for their stones without concurrent biochemical studies. Even in children, it can take a long time to make a diagnosis, and delays can result in long-term kidney impairment. Recurrent stone formers may just be viewed as typical for individuals with stone illness and not deserving of treatment because there is an old proverb that says, "Once a stone former, always a stone former [5].

In some cases, a gene abnormality may predispose a person to renal stones, as in the case of renal tubular acidosis, causing an accumulation of an insoluble substance as a direct result of the lack of an enzyme or a transporter. The entire number of genes involved is still unknown, however a recent study (excluding underlying systemic disease and drug-related stones) targeted 30 known "stone" genes in a renal stone clinic and found mutations in 15% of the families examined, slightly under 21% of pediatric cases, and 11% of adult cases. The most prevalent condition was cystinuria, which is brought on by *SLC7A9* mutations [6].

## LITERATURE REVIEW

### Abnormality in a metabolic pathway

This kind of metabolic illness is exemplified by disorders of purine metabolism that result in deficiencies of the enzymes Adenine Phosphoribosyl Transferase (APRT) and Xanthine Dehydrogenase (XDH). In both situations, they cause a buildup of precursors right before the enzyme block. When APRT is absent, adenine builds up and is converted by XDH into 2,8-Dihydroxyadenine (DHA), whereas XDH deficiency causes xanthine to build up. DHA and xanthine both create nearly pure, radiolucent stones and are extremely insoluble. The non-specific wet chemical technique that makes use of Folin's reagent reduction [7].

In order to identify uric acid, (phosphotungstate/phosphomolybdate) also yields positive results for DHA and xanthine; hence, kidney stone analysis may yield an inaccurate result unless a physical method is applied. Infrared spectroscopy yields a more trustworthy answer, but even here, it takes a skilled operator to be able to identify the type of stone. Very low serum uric acid may also be a sign of XDH, providing the patient is not taking uricase inhibitors. Measurement of pertinent urine purine metabolites and, for APRT, red cell enzyme activity can be used to confirm the presence of both illnesses. They are both autosomal recessive disorders. On the long arm of chromosome 16, the APRT gene, which encodes the APRT enzyme, is

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located. To date, more than 40 variants have been identified, some of which are more prevalent in certain populations. For instance, the mutation p.Met136Thr, which has less than 10% of the expected activity, has been discovered in more than 79% of Japanese patients. The mutation that causes improper splicing and is the most prevalent (40%) in a French cohort is c.400+2dup, whereas the second-most prevalent mutation in Caucasians and one that is particularly prevalent in Iceland is c.194A>T (p.Asp65Val). According to enzyme research, heterozygosity for the condition is thought to be 1/100, indicating that the abnormality might not be as uncommon as originally believed.

This illness has an adverse effect on the kidneys that renal transplantation cannot reverse.

### Conversion to an insoluble product

A prime example of this specific kind of stone production is the Primary Hyperoxalurias (PH). There are three recognized varieties of PH, and all three cause the metabolism of precursors to the insoluble calcium oxalate that forms kidney stones or nephrocalcinosis. The common stone type is 100% calcium oxalate, frequently monohydrate suggesting quick production, and in PH1 cases have a unique morphology. However, it is also possible for the stone to have some calcium phosphate. The three varieties, known as PH1, PH2, and PH3, are all autosomal recessive diseases brought on by a lack of the enzymes alanine: Glyoxylate aminotransferase, glyoxylate/hydroxypyruvate reductase, and hydroxyoxoglutarate aldolase, which are respectively encoded by the *AGXT*, *GRHPR*, and *HOGA1* genes [8].

The excretion of oxalate in the urine varies considerably among the three illnesses but is similar. Concentrations above 0.7 mmol urine oxalate/day have been proposed as a reasonable threshold at which to consider a primary cause (in children, the result should be expressed/1.73 m<sup>2</sup>), but this does not necessarily exclude secondary causes, such as bariatric surgery or chronic pancreatitis, nor does a concentration below this exclude PH, so additional tests must be carried out if there is still a strong clinical suspicion. We set up a primary hyperoxaluria metabolites screen (OCM) as a further step for the investigation of this disease after discovering elevated levels of 4-Hydroxy-2-Oxoglutarate (HOG) and dihydroxyglutarate in urine from individuals with PH3.

This analysis can focus genetic testing by offering more evidence for the several major hyperoxalurias, including high glycolate (found in 70% of PH1), glycerate (found in >95% of instances of PH2), and dihydroxyglutarate (discovered in all cases of PH3 to date). Since HOG is unstable unless collected into acidified urine, it is a less accurate marker and could result in a false negative test. In our experience, PH1 is the most prevalent of the three disorders, accounting for around 80% of cases, with PH2 and PH3 accounting for about 10% of cases each. The three disorders occur at similar ages, with the majority beginning in early childhood, at around 5 years of age [9,10].

### Transport failure

A Heteromeric Amino Acid Transporter (HAT) reabsorbs cystine and other cationic amino acids principally across the apical membrane of the proximal renal tubule and jejunal epithelial cells in exchange for intracellular neutral amino acids. A disulphide link connects the heavy and light chains of the HAT at the extracellular surface. The rBAT heavy chain, encoded by *SLC3A1*, and the b0,+AT light chain, encoded by *SLC7A9*, make up the cystine transporter.

Cystinuria, a disorder marked by increased urine excretion of cystine, lysine, ornithine, and arginine, can result from mutations in either gene. Normal fractional excretion of cystine is only 0.4%; however, in cystinuria, this increases to 100%. The other basic amino acids are also significantly lost, but cystine is the least soluble and is the pathophysiology of the disease, contributing for up to 8% in children.

While 90% of cystine is reabsorbed in sections 1 derangement of a metabolic pathway and 2, diversion to an insoluble product of the proximal convoluted tubule, the distribution of rBAT and the light chain b0,+AT are not exactly in line; rBAT is most prevalent in the S<sub>3</sub> segment with less in

the S<sub>2</sub> and S<sub>1</sub> segments, whereas b0,+AT shows the opposite distribution and is primarily found in the S1. Aspartate/Glutamate Transporter 1 (AGT1), a new light chain protein that appears to work in conjunction with rBAT in other regions of the proximal tubule and may help reabsorb any remaining cystine further down the proximal tubule, has recently been identified. Another probable underlying cause of cystinuria is mutations in the gene encoding this protein. Chromosomes 2 and 19 respectively include the *SLC3A1* and *SLC7A9* genes. While mutations in both genes have been reported, *SLC7A9* mutations are more frequent and are thought to be responsible for 21% of children cases and 11% of adult cases in one cohort. There are three different phenotypes: Type A, caused by mutations in both *SLC3A1* alleles, type B, caused by mutations in *SLC7A9*, and type AB, induced by mutations in both genes. Mutations in *SLC7A9* may cause heterozygotes to excrete more cystine. An initial urine screening test based on color development with nitroprusside in the presence of sodium cyanide is necessary for the diagnosis of the condition.

Numerous patients from various ethnic backgrounds have undergone genetic analysis of the relevant genes. The most frequent mutation is the p.Met467Thr variant, which accounts for 30% of mutant *SLC3A1* alleles and the p.Gly105Argc variant, which accounts for 20% of mutations in *SLC7A9*. It is debatable whether genetic testing is always necessary to confirm the diagnosis because it has no impact on how the problem is treated, but it does have the advantage of allowing for the confirmation or exclusion of the disease in other family members.

This disease is treated by alkalinizing urine with potassium citrate to enhance cystine solubility, a potentially unpleasant procedure. To try to keep the level of cystine in the urine under 1200 mol/L, aggressive hydration is also performed, asking patients to consume at least 3L of water spread out throughout the day and night. There are medications that bind cysteines, such as penicillamine and tiopronin. Cystine stones are quite resistant to extracorporeal shock wave lithotripsy; if they are causing obstructions, they may need to be surgically removed. Renal impairment is frequent in cystinuria, with 64% of patients having stage 2 CKD, according to one study.

## DISCUSSION

### A renal tubular acidosis

In the excretion of H<sup>+</sup> ions and water, the renal tubule is crucial. Most disruptions to this control are acquired, such as excessive ADH excretion in reaction to pain or myeloma deposition causing renal tubular acidosis. However, there are a few primary renal tubule cell diseases that are linked to the development of renal stones. In the case of Renal Tubular Acidosis (RTA), stones form for three reasons. First, intracellular acidosis causes the proximal tubule to reabsorb citrate more frequently. Citrate is a natural inhibitor of the production of crystals and stones because it chelates calcium. Second, the systemic acidity causes calcium to be released from bones.

Thirdly, RTA is characterized by the production of alkaline urine that encourages calcium phosphate precipitation. Mutations in the transmembrane protein basolateral anion (Cl/HCO<sub>3</sub>) exchanger AE1, which is encoded by the gene *SLC4A1* on chromosome 17, can result in a dominantly inherited distal RTA. Two transcripts are produced by this gene from two distinct promoters. The erythrocyte membrane expresses the longer transcript, which has an extra 65 amino acids at the N-terminus, while the renal tubule intercalating cells express the shorter transcript.

On the basolateral side of the -intercalated cells of the distal renal tubule in the kidney, AE1 is expressed. The illness phenotype includes nephrocalcinosis and occult acidosis in addition to significant stone formation and growth retardation. The pH of urine cannot ever be reduced below pH 5.5. This condition is also linked to hypokalaemia.

Three mutations that impact this specific amino acid, Arg589, have been identified as a mutation hot zone (p.Arg589His, p.Arg589Ser, p.Arg589Cys). In exons 11 and 15 of the gene, a collection of deletion mutations spanning 16 to 61 base pairs has also recently been reported in Iranian individuals. However, expression in polarized cells revealed that

these proteins were retained intracellularly and in some cases rapidly destroyed. Mutant proteins expressed in xenopus oocytes demonstrated normal anion transport. Other mutants were discovered to be expressed in the apical and basal membranes of polarized cells, including p.Arg901X, p.Met909Thr, and p.Gly609Arg.

### CONCLUSION

As stated in the opening, the goal of this paper was not to be exhaustive but rather to provide a taste of how molecular genetics has infused life into the study of renal stone disease, enhanced diagnostics, and broadened our fundamental understanding of physiological processes. As whole genome approaches are used to study stone formers and their families, more genetic factors of kidney stone formation will probably become apparent over the next years. Why some people have a considerably more severe course than others even if they appear to have the same degree of metabolic abnormalities is still a mystery. It will likely take knowledge of genetics, proteomics, chemistry, and biochemistry to provide a solution to this question.

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