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Review

Genetic defects underlying renal stone disease

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HIGHLIGHTS

- The molecular basis of 4 inherited renal stone disorders is described.
- The underlying cause of renal stone formation is different for each disorder presented.
- The importance of detection of these disorders is emphasised for renal health and that of other family members.

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ABSTRACT

Renal stones are common and are usually secondary to risk factors affecting the solubility of substances in the urinary tract. Primary, that is genetic, causes are rare but nevertheless are important to recognise so that appropriate treatments can be instigated and the risks to other family members acknowledged.

A brief overview of the investigation of renal stones from a biochemical point of view is presented with emphasis on the problems that can arise.

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 is described by reference to the disorders of adenine phosphoribosyl transferase (APRT) deficiency, primary hyperoxaluria, cystinuria and autosomal dominant distal renal tubular acidosis.

Renal stones (nephrolithiasis) are common, with various estimates that they affect from 6 to 15% of the population in the western world [1]. In the majority of cases these relate to environmental risk factors including occupation, diet, low fluid intake, lack of stone inhibitors, administration of insoluble drugs, e.g. antiretrovirals; or to acquired disease such as hyperparathyroidism or anatomical factors, e.g. horseshoe kidney. Nephrocalcinosis is a related disorder that may also indicate precipitation of calcium in the kidney. In a small but significant proportion nephrocalcinosis and nephrolithiasis are the result of inherited disease, autosomal dominant, recessive or X-linked disorders, and their detection has implications for disease prognosis, treatment and risks to other family members. This review will focus on the inherited disorders of renal stone disease. It is not intended to be fully inclusive as this would be impossible with an ever expanding list of disorders, but will focus on some reasonably well defined metabolic causes that are examples of (i) derangement of a metabolic pathway, (ii) diversion to an insoluble product, (iii) failure of transport and (iv) renal tubular acidosis.

Suspicion of an inherited cause of renal stone disease should be raised by any of the following factors: early age of onset, recurrent stones, bilateral stone disease, family history or history of consanguinity. The support for initial investigations (Table 1) can be provided by most clinical biochemistry laboratories either in-house (for the majority of tests) or by referral to specialist centres (oxalate, citrate, cystine, primary hyperoxaluria metabolites). Analysis of the kidney stone, if available, can be helpful [2] although data from an external quality assurance scheme run by my laboratory suggests that not all laboratories provide a reliable service in this regard, in some cases regularly misidentifying stone types, failing to identify other rare stone types and giving no indication of the relative contribution of the different components. Tests that use physical analysis, e.g infra-red, are more likely to give reliable results. Radiographic analysis will identify whether stones *insitu* are calcium containing (radio-opaque) or radiolucent, the latter pointing to uric acid or other purine material or only faintly radio-dense as seen with cystine-containing stones. Stone disease in children is

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Table 1
Investigations for renal stone disease.

Initial investigations	24 h urine (plain)	24 h urine (acid collection)
	Volume	Volume
	creatinine	creatinine
	urate	calcium
	protein	magnesium
	pH	citrate
	Cystine (spot test)	oxalate
Secondary investigations	Cystine (quantitation) if spot test positive	Primary hyperoxaluria metabolites (glycolate, glycerate, HOG and DHG)

more likely to be investigated by a metabolic profile but sadly the same is often not done in the adult where stones may simply be physically treated without concurrent biochemical investigations. Even in children it can take a significant amount of time for a diagnosis to be made, with delays contributing to long term renal damage.There is an old adage 'once a stone former always a stone former' and thus recurrent stone formers may simply be regarded as typical for patients with stone disease and not deserving of closer inspection.

Renal stones may be a direct effect of loss of an enzyme or a transporter leading to accumulation of an insoluble substance, while in others the gene defect may predispose the individual to renal stones, as for example in renal tubular acidosis. The total number of genes involved is as yet unknown but a recent study targeted 30 known 'stone' genes in consecutive patients in a renal stone clinic (excluding primary systemic disease and drug-related stones) and identified mutations in 15% of the families studied, just under 21% of paediatric cases and 11% of adults [3]. Cystinuria, caused by mutations in *SLC7A9* was the most common disorder.

1. Derangement of a metabolic pathway

Disorders of purine metabolism leading to deficiency of the enzymes adenine phosphoribosyl transferase (APRT) and xanthine dehydrogenase (XDH) are illustrative of this type of metabolic disorder. In both cases they lead to an accumulation of precursors immediately prior to the enzyme block. In the case of APRT deficiency, adenine accumulates and is metabolised to 2,8-dihydroxyadenine (DHA) by XDH; while lack of XDH leads to an accumulation of xanthine. DHA and xanthine are both highly insoluble and form almost pure, radiolucent stones. The non-specific wet chemical method that uses the reduction of Folin's reagent (phosphotungstate/phosphomolybdate) for detection of uric acid also gives a positive result with DHA and xanthine and therefore kidney stone analysis may give an incorrect result unless a physical method is used (Fig. 1). A more reliable result is obtained by infra-red spectrometry (Fig. 1) but even here, it requires an experienced operator to be able to confirm the stone type. XDH may also be suspected by very low serum uric acid assuming the patient is not receiving uricase inhibitors. Confirmation of both disorders can be made by measurement of relevant urine purine metabolites and for APRT, the measurement of enzyme activity in red cells [4].

Both diseases are autosomal recessive. The APRT enzyme is encoded by *APRT*, a gene on the long arm of chromosome 16 (16q24) [5]. More than 40 mutations have been described to date with some common to particular populations, e.g.p.Met136Thr with less than 10% of normal activity [6] has been found in over 79% of Japanese patients [7]. The most common mutation (40%) in a French cohort was c.400+2dup that leads to incorrect splicing [8] whereas c.194A > T (p.Asp65Val) is the next most common in Caucasians and is particularly common in Iceland [9]. Heterozygosity for the disorder, as estimated from enzyme studies, is thought to be 1/100 [10] suggesting that the defect may not be as rare as previously thought. This suggestion is supported by the finding of the c.400+2dup mutation in 1% of healthy newborns [8] and may in fact either present later in life or be incorrectly diagnosed as uric acid lithiasis as a result of inaccurate stone analysis. End stage renal failure is a consequence of this disorder that is not corrected by renal transplantation.

2. Diversion to an insoluble product

The primary hyperoxalurias (PH) are a perfect illustration of this particular type of stone formation. There are three known types of PH, all of which lead to metabolism of precursors to insoluble calcium oxalate that precipitates in the kidney as nephrocalcinosis or renal stones. The stone type is typically 100% calcium oxalate, often monohydrate indicating rapid formation and in cases of PH1 have an unusual morphology [11] but can also be mixed with calcium phosphate. The three types, PH1, PH2 and PH3, are all autosomal recessive disorders and are caused by deficiency of alanine:glyoxylate aminotransferase, glyoxylate/hydroxypyruvate reductase and hydroxyoxoglutarate aldolase enzymes (Fig. 2) encoded by *AGXT*, *GRHPR* and *HOGA1* genes respectively.

Urine oxalate excretion is similar in the three disorders and can be quite variable [12]. Concentrations greater than 0.7 mmol urine oxalate/day [13] have been suggested as a reasonable level at which to consider a primary cause (in children, the result should be expressed/1.73 m^2) but this does not necessarily exclude secondary causes, such as bariatric surgery [14]or chronic pancreatitis, neither does a concentration below this exclude PH so if still strong clinical suspicion additional tests need to be performed. The finding of increased 4-hydroxy-2-oxoglutarate (HOG) and dihydroxyglutarate in urine from patients with PH3 [15, 16] led us to set up a primary hyperoxaluria metabolites screen (OCM) as a next step for the investigation of this disease (Table 1). This analysis can provide additional support for the different primary hyperoxalurias: elevated glycolate (found in 70% of PH1), glycerate (found in >95% cases PH2) and dihydroxyglutarate (in all cases of PH3 to date) and therefore focus genetic testing. HOG is a less reliable marker as it is unstable unless collected into acidified urine and may therefore yield a false negative result [17]. PH1 is the more common of the three diseases accounting for approximately 80% of cases in our experience [18], PH2 and PH3 accounting for around 10% each. The age of presentation for the three disorders is similar with most presenting in early childhood, around 5y of age [19].

AGXT occurs in two allelic forms, the major and minor alleles, the latter encoding a protein with an amino acid change, p.Pro11Leu that has approximately 60% activity of the major [20]and introduces a weak mitochondrial targeting sequence [21,22]. The minor allele occurs at a frequency of approximately 20% in Europeans but is much less common in African Americans [23].Mutations occurring on the background of the minor allele tend to have lower activity and stability [24,25] at least *in vitro*. More than 170 mutations have been described (see www.uclh.nhs.uk/phmd), in most cases leading to considerable reduction or complete loss of enzyme activity [20]. The majority are single nucleotide changes

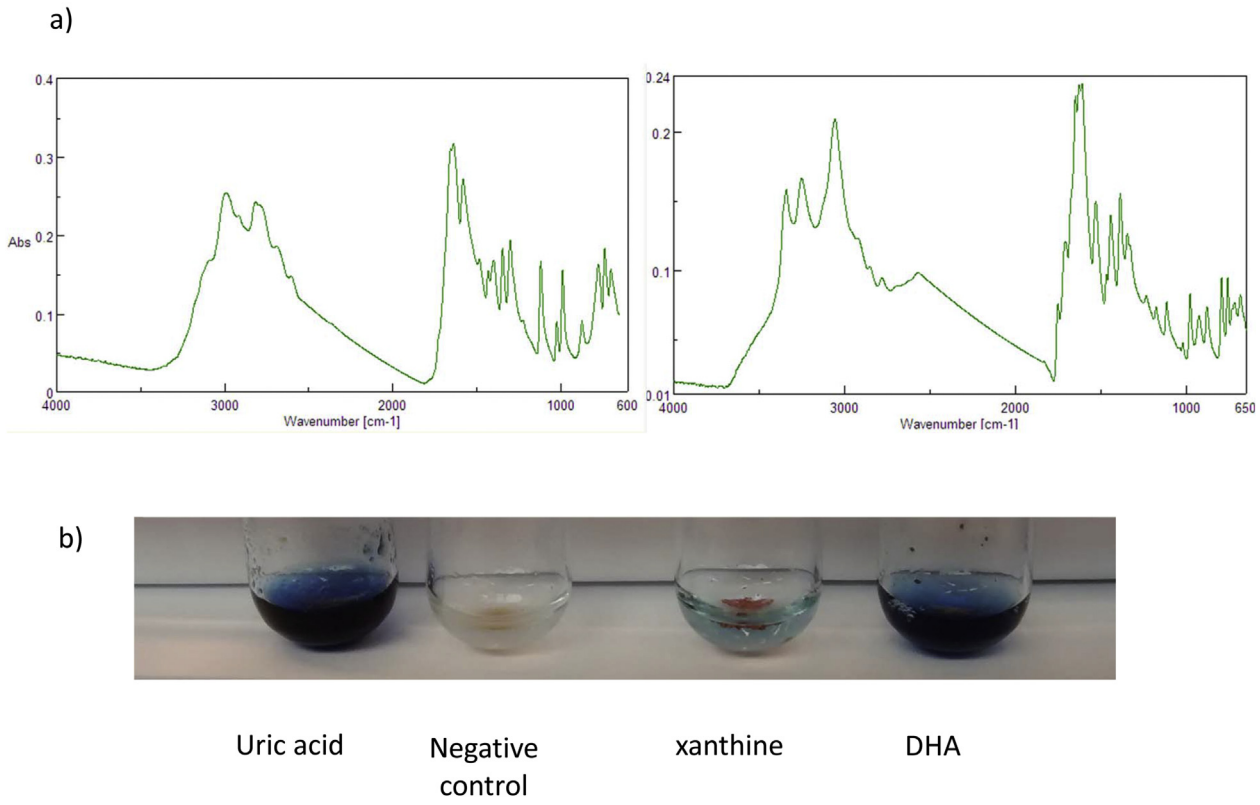

Fig. 1. a) Fourier transform infra-red spectrum of uric acid (left) and DHA (right) showing obvious difference in spectral properties. b) Folin's reagent (phosphotungstate/phosphomolybdate) test for uric acid also shows positive results (blue colouration) with xanthine and DHA.

with c.508G > A (p.Gly170Arg) occurring in up to 30% of mutant alleles across all patient populations described [20]. This mutant retains significant activity *in vitro* but has the effect of slowing dimerization of the protein, with the result that the enzyme is mistargeted to the mitochondrion where it is unable to fulfil its role in glyoxylate detoxification [26]. Patients with this mutation and the p.Phe152Ile variant may be responsive to pyridoxine supplementation [27] (pyridoxine is a cofactor for alanine:glyoxylate aminotransferase enzyme).In some cases, in conjunction with hydration, pyridoxine will bring urine oxalate excretion to within the reference range [27] and can have an impact on transplantation outcome [28]. The biological variation of urine oxalate is high and consequently a reduction of at least one-third is required to constitute a significant change [29].

Mutations in GRHPR are quite varied but there are two common changes, both leading to missplicing.The first,c.103delG [30,31], is almost exclusively found in Caucasians, accounts for 37% mutations in our patient cohort [31] and has a carrier frequency of 1:375 [23].The second is a 4 base pair deletion, c.[403_404+2delAAGT] [30,31], is found predominantly in Asians, causes missplicing of mRNA and accounts for 18% mutant alleles [31].

PH3, the results of mutation in*HOGA1,* has only recently been described [15] but there are two common pathological variants.One,a 3bp deletion (c.944_946delAGG, p.Glu315del) [15] is prevalent in the Ashkenazi Jewish population. The other, c.700+5G > T, has been found in several patient cohorts [15,19]and demonstrated to cause missplicing in hepatic RNA [19] and *in vitro* [15]. From analysis of public whole exome databases, the carrier frequency of this mutation (1:165) is much higher than would be expected for the frequency of the disease [23]and in our patient cohort we found 3 heterozygotes for this mutation in patients with confirmed PH1 [32]. This finding does have implications for genetic diagnosis (see below).

Genetic testing is available for all three disorders and provides confirmation of biochemical testing, allows prenatal diagnosis and the confirmation/exclusion of disease in other family members. This latter point is of considerable importance as all three types may remain clinically hidden until adulthood although all affected are at risk of sudden onset of renal failure. As renal transplantation is part of the treatment plan for PH1 and PH2, in the former usually recommended following liver transplantation [33], the use of a living related kidney from within the family needs careful exclusion of cryptic disease in such a potential organ donor. The caveat for genetic testing is that, in view of the findings from next generation sequencing mentioned above, the occurrence of a single mutation plus hyperoxaluria can no longer be regarded as definitively diagnostic for any of the primary hyperoxalurias.

Another inherited cause of calcium oxalate stones has recently been described as a result of mutations in the SAT1 sulphate-oxalate transporter, encoded by *SLC26A1* [34]. Hyperoxaluria was present but not excessively so. However, this finding may provide an explanation for those patients with suspected inherited hyperoxaluria in whom the three known forms of PH have been excluded.

3. Failure of transport

The amino acid cystine, along with other cationic aminoacids, is reabsorbed primarily across the apical membrane of the proximal renal tubule and jejeunal epithelial cells by a heteromeric amino acid transporter (HAT) in exchange for intracellular neutral amino acids. The HAT is composed of a heavy and a light chain joined on the extracellular surface by a disulphide bond. The cystine transporter is composed of the rBAT heavy chain, encoded by *SLC3A1* [35]and $b^{0,+}$AT light chain encoded by *SLC7A9* [36]. Mutations in either gene can give rise to the condition of cystinuria,

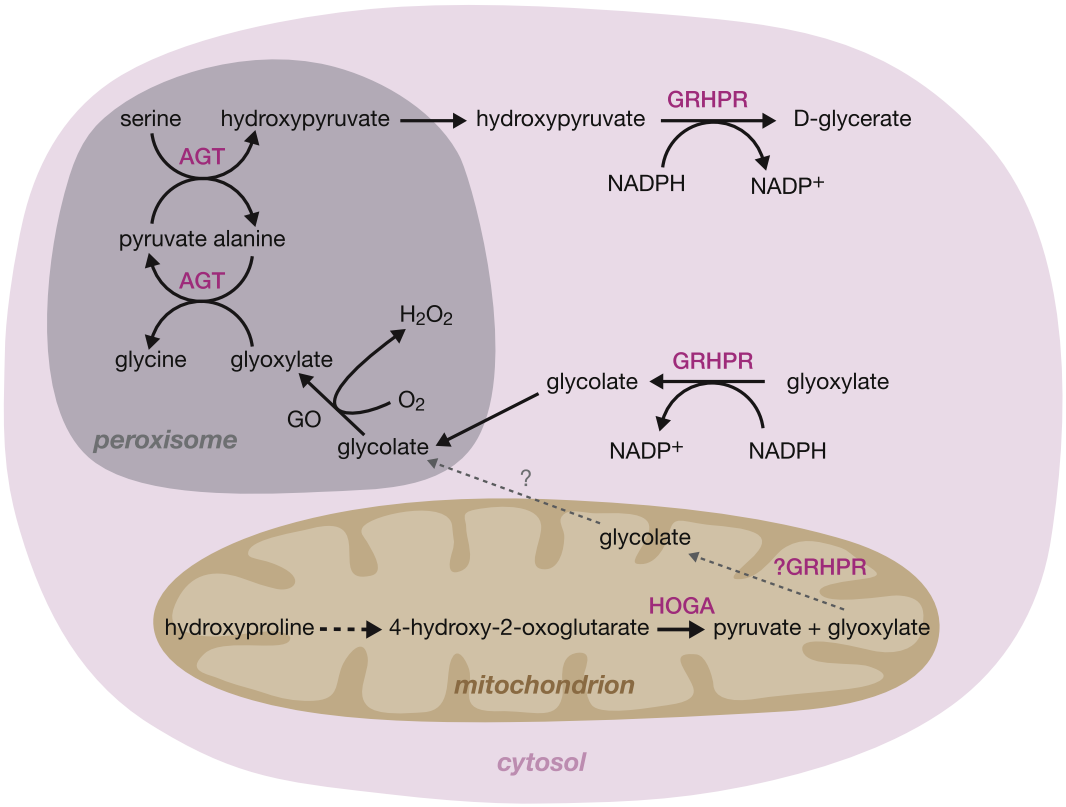

Fig. 2. Glyoxylate metabolism in the hepatocyte. Glyoxylate is metabolised by alanine:glyoxylate aminotransferase (AGT) in the peroxisomes and by glyoxylate/hydroxypyruvate reductase (GRHPR) in the cytosol. Deficiency of these enzymes causes PH1 and PH2 respectively. In both cases excess glyoxylate is metabolised to oxalate by lactate dehydrogenase. Hydroxyoxoglutarate aldolase (HOGA) in the mitochondria is defective in PH3. The mechanism of hyperoxaluria in this disorder is still unclear but may reflect breakdown of HOG.

characterised by high urinary excretion of cystine, lysine, ornithine and arginine. The fractional excretion of cystine is normally only 0.4% but this rises to 100% in cystinuria. There is also significant loss of the other basic amino acids but cystine is the least soluble and therefore causes the disease pathology, accounting for up to 8% in children [37]. While 90% of cystine is reabsorbed in sections S1 and S2 of the proximal convoluted tubule, the distribution of rBAT and the light chain $b^{0,+}$AT are not perfectly aligned; rBAT is most abundant in the S3 segment with less in the S2 and S1 segments whereas $b^{0,+}$AT shows the reverse distribution and is mainly found in the S1 [38]. Another light chain protein, aspartate/glutamate transporter 1 (AGT1), has recently been described that appears to act in association with rBAT in other parts of the proximal tubule and may act to reabsorb any residual cystine further down the proximal tubule [39]. Mutations in the gene encoding this protein may potentially be another underlying cause of cystinuria.

The *SLC3A1* and *SLC7A9* genes are found on chromosomes 2 [40] and 19 [41] respectively. Mutations have been described in both genes but most commonly in *SLC7A9*, recently estimated to account for 11% of adults and 21% childhood cases in one cohort [3]. There are three phenotypes, type A where both alleles of *SLC3A1* are mutated, type B caused by mutations in *SLC7A9* and type AB where one mutation is found in one gene and one in the other. Heterozygotes for mutations in *SLC7A9* may show an increased excretion of cystine. Diagnosis of the disorder requires an initial urine screening test based on colour formation with nitroprusside in the presence of sodium cyanide. This screen can yield false positive results with homocystine and sulphur-containing drugs and therefore qualitative analysis should be followed up with quantitation of urine amino acids. Homozygotes for cystinuria excrete >1300 μmol cystine per day (normal <100).

Genetic analysis of the respective genes has been performed in a large number of patients across different ethnic groups.The p.Met467Thrvariant is the most common mutation accounting for 30% mutant*SLC3A1*alleles whilep.Gly105Argaccounts for 20% of mutations in*SLC7A9*(for review see reference [42]). It is a moot point whether genetic analysis is required in all cases to confirm the diagnosis as it does not affect treatment of the disorder but it does have the advantage of being able to confirm/exclude the disease in other family members.

Treatment of this disorder uses alkalinisation of urine with potassium citrate to increase cystine solubility,a treatment that may not be well tolerated. Aggressive hydration is also used requiring patients to drink at least 3L of water spread throughout the day and night to try to keep the concentration of cystine in urine below 1200 μmol/L. Cystine binding drugs are available, e.g. penicillamine and tiopronin. Cystine stones are quite resistant to extracorporeal shock wave lithotripsy and therefore may need to be removed surgically if causing blockages. Renal impairment is not uncommon in cystinuria with one study reporting 64% in CKD stage 2 [43].

4. Renal tubular acidosis

The renal tubule plays a major role in water and H^+ ion excretion. The majority of disturbances to this regulation are acquired, e.g. excess ADH excretion in response to pain; myeloma deposition leading to renal tubular acidosis. There are, however, some primary disorders of renal tubule cells that are associated with renal stone formation. In the case of renal tubular acidosis(RTA), stone formation occurs for three reasons, firstly the intracellular acidosis leads to increased reabsorption of citrate by the proximal tubule. Citrate

chelates calcium and is a natural inhibitor of crystal and stone formation. Secondly, calcium is released from bones as a consequence of the systemic acidosis. Thirdly RTA is characterised by production of alkaline urine that favours the precipitation of calcium phosphate. One example of a dominantly inherited distal RTA is caused by mutations in the basolateral anion ($Cl^-/HCO3^-$) exchanger AE1, a transmembrane protein encoded by *SLC4A1* located on chromosome 17 [44]. This gene gives rise to two transcripts from different promoters [45]. The longer transcript that includes an additional 65 amino acids at the N-terminal is expressed in the erythrocyte membrane while the shorter one is found in the intercalating cells of the renal tubule [46]. In the kidney AE1 is expressed on the basolateral side of the α-intercalated cells of the distal renal tubule. The disease phenotype ranges from severe stone formation with growth retardation through to occult acidosis and nephrocalcinosis. In all cases, urine pH cannot be acidified below pH5.5. Hypokalaemia is also associated with this disorder.

A mutation hot spot has been described at Arg589, with three mutations affecting this particular amino acid (p.Arg589His, p.Arg589Ser, p.Arg589Cys) [47].In addition, a cluster of deletion mutations ranging from 16 to 61 base pairs has recently been described in Iranian patients in exons 11 and 15 of the gene [48]. Mutant proteins expressed in Xenopus oocytes showed normal anion transport [47] but expression in polarised cells showed that these proteins were retained intracellularly [49] and in some cases rapidly degraded [50]. Other mutants, notably p.Arg901X, p.Met909Thr and p.Gly609Arg, were found to be expressed in the apical and basal membranes of polarised cells [49,51–53]. The p.Arg901X mutation arises from a loss of the last 11 amino acids of the protein [54] providing evidence for a targeting sequence in the carboxyterminal of the protein [52], although this signal is not sufficient on its own and there may also be N-terminal sequences required for efficient targeting to the basal membrane [53].

One interesting question is how these mutations cause a dominantly inherited disease in view of their apparent lack of an effect on anion transport. The protein is a dimer and thus would be expected to form heterodimers of one normal and one mutant subunit with sequestration of the heterodimer intracellularly in the case of the p.Arg589His and Gly701Asp mutants [49,50]. The mistargeting of the heterodimer to the apical membrane leads to expression in the wrong membrane location, with bicarbonate excretion into the lumen that effectively negates acid secretion [49].

5. Conclusion

As mentioned in the introduction, this article has not tried to be comprehensive, rather it has aimed to give a flavour of how molecular genetics has enlivened the field of renal stone disease, improved diagnostics and increased our basic knowledge of physiological processes. The next few years will undoubtedly reveal more genetic causes of kidney stone formation as whole genome methods are applied to stone formers and their families. What is still not addressed is why, with apparently the same degree of metabolic abnormality, some individuals follow a much more severe course than others. To answer this question will probably require a combination of genetics, proteomics, chemistry and biochemistry.

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Gill Rumsby is Author.

Conflicts of interest

None.

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Gill Rumsby.

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