REVIEW

A review of the heritability of idiopathic nephrolithiasis

D G Griffin

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Familial aggregations of nephrolithiasis were already noted in the early 19th century and over the intervening years there has been gradual progression in classifying the familial forms of nephrolithiasis. To date, there are at least 10 different monogenic conditions where those affected have a predisposition to nephrolithiasis. However, all of these rare conditions probably account for less than 2% of renal stone formers. This review, rather than considering these clearly defined disorders, concentrates on research into the broad band of stone formers who have a propensity to nephrolithiasis without an obvious discrete genetic basis.

Kidney stones are common, affecting up to 5% of the population.¹ Among men,^{2,3} the lifetime risk may be as high as 7.8%.⁴ It is a disease that often affects young people, with a peak age of first presentation of around 28 years in men and 35 years in women.⁴ In addition to the morbidity of a very painful condition, the very high recurrence rate for renal stone disease (over 50% have a recurrence within eight years^{1,5}) means that it can be a source of considerable anxiety and even depression to the habitual stone former.

Familial aggregations of nephrolithiasis had already been noted in the early 19th century,⁶ and over the intervening years there has been a gradual progression in classifying the familial forms of nephrolithiasis. To date, there are at least 10 different monogenic conditions, such as cystinuria, primary hyperoxaluria, renal tubular acidosis, and Dent's disease, where those affected have a predisposition to nephrolithiasis. However, all of these rare conditions probably account for less than 2% of renal stone formers. This review, rather than considering these clearly defined disorders, concentrates on research into the broad band of stone formers who have a propensity to nephrolithiasis without an obvious discrete genetic basis.

Familial risk for idiopathic nephrolithiasis

The first clues that idiopathic nephrolithiasis might have a large genetic component were based on its clustering in families. As early as 1894, reports on familial aggregations of urinary calculi were recorded.⁷ A detailed early family study including 15 stone formers was reported by Gram in 1932.⁸

These studies provided the impetus for some retrospective case-control studies, to determine the relative importance of heredity and

environment in idiopathic nephrolithiasis. McGeown provided the first large sample, retrospective, case-control study by collecting data on 174 patients with renal stones and 174 age and sex matched controls.⁹ She found a significant increase in the number of parents and siblings with kidney stones among the stone forming group compared with controls.

McGeown's findings pointed to a familial risk for renal stone disease, but she did not attempt to quantify the increase in renal stone risk associated with a family history. A useful quantitative epidemiological measure of familial risk is the relative risk, λ_R , whereby one determines whether individuals with an affected relative have a higher risk than the general population.¹⁰ An evaluation of relative risk from McGeown's data, using the relatives of controls to represent risk in the general population, results in a λ_R of ~ 16 for parents (that is, parents with children who are stone formers are 16 times more likely to have renal stone disease than the general population) and for siblings.

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Although this analysis of McGeown's data suggests a large familial risk associated with renal stone disease, some caution is required before accepting these results. The controls were selected specifically as non-stone formers and therefore do not represent the normal population. In theory, the relatives of a cohort of non-stone forming individuals would probably have a reduced relative risk compared with the population as a whole. Therefore, comparing these two groups probably accentuates the relative risk for the relatives of stone formers.

Resnick and colleagues¹¹ and Trinchieri and colleagues¹² performed similar studies but attempted to overcome the shortcomings of McGeown's study by using the spouses of stone formers as a control group. Although the sizes of the relative risks were not as impressive, they were able to show a significantly higher frequency of relatives with stones in the stone forming group. Using the relatives of spouses as controls, Resnick's data reveals that fathers have a λ_R of ~ 4 , mothers and brothers have a λ_R of ~ 3 , and sisters have a λ_R of ~ 2 . Similarly, Trinchieri's data points to a λ_R of ~ 3 for all first degree relatives.

Many diseases are thought to arise when a certain "threshold" of genetic and environmental factors has been surpassed. Falconer¹³ conceptualised this as a normally distributed

Correspondence to:
Dr D G Griffin, Department
of Chemical Pathology,
Morriston Hospital,
Swansea SA6 6NL, UK;
damian.griffin@
swansea-tr.wales.nhs.uk

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polygenically and environmentally determined risk, known as liability, with a qualitative trait appearing in persons whose liability exceeds some threshold value. Falconer modelled the heritability (h^2) of liability to nephrolithiasis using data on the incidence of disease among relatives of probands and the incidence among relatives of controls. In other words, one can calculate the fraction of the liability to nephrolithiasis that has a genetic basis. Using McGee's data,⁹ Falconer established an estimate of the heritability of the liability to renal stone disease at $h^2 = 46 \pm 9\%$. Using the same methods on male siblings of probands and controls, Resnick *et al* estimated the heritability of the liability to disease at $h^2 = 63 \pm 14\%$.¹¹ These results suggest that if one accepts Falconer's model of a normally distributed polygenically and environmentally determined liability underlying nephrolithiasis, about half the liability has a genetic basis. It should be pointed out that Falconer, when modelling the heritability of disease, made several assumptions. Importantly, he assumed that the relatives of probands had a similar distribution of environmental factors affecting their liability to disease as the general population. This may not be entirely true because the kindred of renal stone formers may have slightly different habits in relation to diet, fluid intake, use of central heating, and so on, compared with the general population. This could potentially result in error in the estimation of the heritability of liability to renal stone disease.

Mode of inheritance of idiopathic nephrolithiasis

The excess of stone formation found among the first degree relatives of probands supports the inference that genetic factors regulate the tendency to idiopathic nephrolithiasis, but it does not indicate the mode of inheritance.

Segregation analysis involves fitting a general model to the inheritance patterns of a trait in families based on Mendel's law of segregation. The idea is to see whether the pattern of phenotypes in families is consistent with a genetic model.¹⁴

The earliest attempt to model the segregation of nephrolithiasis was performed by Gram on his four generation renal stone family.⁸ He concluded that it was probably an autosomal dominant condition, although he failed to explain why some individuals did not fit in with the proposed model.

"It is probable that there is considerable genetic heterogeneity in renal stone disease"

Of course, at the time that Gram was hypothesising, the understanding of the relation between genes and disease stemmed from uncommon or rare monogenic disorders. It is now accepted that renal stone disease has a far more complex mode of inheritance and a wide number of effects need to be considered when modelling its mode of inheritance.

As we know, renal stone disease often does not manifest itself until midlife.¹⁵ This means that many susceptible individuals in a collection of multigenerational families segregating stone disease will be disease free at the time of investigation. When modelling the mode of inheritance based on a cohort of pedigrees one has to take account of the incomplete penetrance of the trait.

Another confounding factor is that many individuals with renal stone disease may never have symptomatic disease. Their stones may go unnoticed throughout life or be diagnosed only as an incidental radiographical finding during investigation of unrelated symptoms. Indeed, radiographical studies have shown a prevalence of 3.5% for renal stone disease among a random population.¹⁶

Apart from a genetic influence, there are environmental or disease related causes of renal stone disease, such as strenuous physical exercise, excessive sweating in a hot

climate, a high sodium diet, a diet rich in animal protein, compromised ileal function, and hyperparathyroidism. Therefore, members of a pedigree who do not inherit a predisposing genotype may nonetheless get the disease (phenocopy).

It is probable that there is considerable genetic heterogeneity in renal stone disease. Mutations in any one of several genes may result in similar phenotypes—for example, if their products are required for a common biochemical pathway or cellular structure.

In addition, it is probable that renal stone disease may require the simultaneous presence of mutations in multiple genes (polygenic inheritance). This may represent a threshold effect, produced whenever an underlying quantitative variable, influenced by multiple genes, exceeds a crucial threshold. Alternatively, it may be a pure synthetic effect, requiring the simultaneous and joint action of each of several mutations. Polygenic inheritance complicates the understanding of the genetic basis for a condition because no single locus is strictly required to produce the phenotypic trait.

The knowledge that the genetic basis of most common disorders is polygenic led Resnick and colleagues¹¹ to test their data to determine whether the observations were compatible with single locus or multiple locus aetiology. They noted that the prevalence of stone disease in the fathers of probands was much lower than expected for dominant inheritance. To test for polygenic inheritance, they compared the number of stone formers in younger siblings of the probands, in which no older siblings were affected, with the number in which one or more older siblings were affected. For monogenic disorders, the risk should be the same for younger siblings, regardless of whether older siblings are affected or not. They found a significantly higher frequency of stone formers when older siblings were affected, suggesting that the susceptibility is polygenic.

Goodman carried out a review of genetic factors in renal stone disease.² They concluded that there was a trimodal distribution of calciuria, oxaluria, and citraturia, suggestive of three genes with codominant alleles. They then proposed a polygenic model of calcium oxalate stone disease based on these three genes being largely responsible for the susceptibility to renal stone disease. However, several speculative assumptions had to be accepted to make their family data fit the chosen model.

Intermediate traits for idiopathic nephrolithiasis

The difficulties in analysing the mode of inheritance of renal stone disease have led to the use of a divide and conquer strategy. From an aetiological perspective, the formation of renal stones is thought to be the culmination of several factors, with many relating to different biochemical abnormalities that may precipitate stone disease. By looking at distinct quantitative biochemical traits associated with renal stone disease, rather than affection status, the complexity of the mode of inheritance can be reduced. These intermediate traits are probably under the influence of fewer genes and their segregation should therefore be easier to model. With this in mind, several investigators have studied the heritability of biochemical abnormalities thought to promote the development of renal stone disease. Among the biochemical characteristics of renal stone formers that have been explored, idiopathic hypercalciuria and idiopathic hyperoxaluria probably show the most promise as heritable traits influencing the liability to stone formation. Their importance in predicting individuals at risk of forming renal stones means that they were a good starting point in the search for suitable intermediate biochemical traits.

Idiopathic hypercalciuria

The term idiopathic hypercalciuria was introduced by Albright and colleagues¹⁷ to describe those hypercalciuric renal stone forming patients with normal concentrations of plasma calcium and a tendency to low phosphate values, who have none of the known causes of normocalcaemic hypercalciuria, such as immobilisation, sarcoidosis, and acromegaly. Further larger scale studies have confirmed that 30–40% of patients who form calcium containing renal stones are hypercalciuric.^{18–20} The pathogenesis of idiopathic hypercalciuria involves excessive intestinal calcium absorption and depressed renal tubule reabsorption. Excessive urine calcium losses are offset by increased intestinal calcium absorption, but not always completely. Calcium balance is negative in almost half the patients and there is evidence of reduced bone mineral density among patients with idiopathic hypercalciuria.^{21–23} It should be pointed out that the validity of this inference is disputed. Some researchers propose that the reduced bone mineral density is a secondary effect related to the low calcium intake of many renal stone formers.²⁴

Coe *et al* examined the family pedigrees of nine probands with idiopathic hypercalciuria.²⁵ They concluded that the occurrence of hypercalciuria within the pedigrees strongly suggested an inherited trait that had segregation characteristics consistent with an autosomal dominant mode of inheritance.

There is much dispute as to whether increased intestinal calcium absorption or reduced renal tubule calcium reabsorption is the primary electrolyte abnormality in idiopathic hypercalciuria. The term idiopathic hypercalciuria includes subclasses of patients who appear to have an underlying defect in renal tubular reabsorption of calcium (renal hypercalciuria) and those with increased intestinal absorption of calcium as the primary abnormality.

Several studies have attempted to establish whether renal or absorptive hypercalciuria is the heritable form. Pak *et al* looked at one large pedigree within which the occurrence of renal stone disease was consistent with an autosomal dominant mode of inheritance.²⁶ Furthermore, they suggested that absorptive hypercalciuria might be an expression of the genetic trait because nephrolithiasis was encountered only in the progeny of members who had stones or biochemical evidence of absorptive hypercalciuria.

Nicolaidou *et al* supported this conclusion in a study of the families of 40 children with idiopathic nephrolithiasis.²⁷ Their data suggest that idiopathic hypercalciuria has both a familial and a sporadic form, with most of the families having the absorptive subtype. An autosomal dominant mode of inheritance appeared to be present.

“Sequence variations in the soluble adenylylase human homologue gene occur with increased frequencies in the absorptive hypercalciuria population”

In contrast, Harangi *et al* looked at the families of 21 children with nephrolithiasis and idiopathic hypercalciuria.²⁸ They concluded that hypercalciuria was more commonly a familial trait where the probands had renal hypercalciuria rather than the absorptive form. Pedigrees of renal hypercalciuric probands were compatible with an autosomal dominant inheritance of hypercalciuria and/or nephrolithiasis. It was suggested that absorptive hypercalciuria was possibly secondary to diet.

Recently, in pedigrees with a severe form of absorptive hypercalciuria, an associated trait has been mapped to chromosome 1q23.3–23.4.²⁹ A follow up study³⁰ has identified sequence variations in the soluble adenylylase human homologue gene that occur with increased frequencies in the

absorptive hypercalciuria population outside the selected families of the initial study. The significance of this is far reaching in that we now have a genetic locus that not only co-segregates with a rare monogenic form of absorptive hypercalciuria, but appears to play a role in more common forms of hypercalciuria.

Hyperoxaluria

Excessive urinary oxalate excretion occurs in some renal stone formers.^{31–32} It causes stones by raising the saturation of the urine with respect to calcium oxalate. The mechanism of hyperoxaluria is either gastrointestinal overabsorption or metabolic overproduction.

Marangella *et al* have shown that oxalate absorption correlates with dietary calcium and urinary calcium excretion in stone formers.³³ This is consistent with a hypothesis that hyperoxaluria is secondary to calcium hyperabsorption. Hyperoxaluria secondary to increased intestinal oxalate absorption may also complicate Crohn's disease, coeliac disease, pancreatic insufficiency, and small intestinal bypass surgery for obesity. Dietary fat malabsorption with steatorrhoea is common to all these conditions, and increased luminal free fatty acids may be crucial in the development of oxalate overabsorption. More recently a correlation between hyperoxaluria, oxalate stone disease, and the absence of the gastrointestinal tract dwelling bacteria *Oxalobacter formigenes* has been reported.³⁴

Primary hyperoxalurias that result from the metabolic overproduction of oxalate are extremely rare. Although it has long been recognised that hyperoxaluria plays an important aetiological role in nephrolithiasis, until recently little consideration has been given to the possibility of a common genetic defect being responsible. Holmes *et al* concluded that the distribution of oxalate excretion values was trimodal,³⁵ possibly reflecting the existence of two allelic genes determining high and low oxalate excretion occurring with frequencies of 0.32 and 0.68, respectively.

Baggio *et al* investigated red blood cell transmembrane oxalate flux in patients with idiopathic calcium nephrolithiasis and controls.³⁶ They noted that the oxalate flux was significantly higher in the patients than in the controls. They also found that the familial aggregation of red blood cell transmembrane oxalate flux was probably of autosomal dominant inheritance with variable penetrance.³⁷ The significance of these findings has yet to be clarified.

CONCLUSIONS

In this review, we have stepped forward from the earliest evidence for a familial risk for renal stone disease, through a

Take home messages

- First degree relatives of stone formers have three times the risk of developing renal stones compared with the general population
- Approximately half of an individual's liability to renal stone disease is genetic and half is environmental
- The available data suggest that the mode of inheritance is complex and polygenic
- Sequence variations in a gene on chromosome 1 may be responsible for the hypercalciuria found in some cases of idiopathic nephrolithiasis
- There is some evidence for a monogenic basis for a small number of cases of idiopathic hyperoxaluria, which predisposes to idiopathic nephrolithiasis

gradual refinement in our understanding of the heritability of renal stone disease and its intermediate traits to the recent discovery of a genetic locus influencing the expression of one of these traits. Although there have been mistakes and misinterpretations along the path, we are now making solid progress in teasing apart the genetic strands that will form the foundations of an accurate genetic model of idiopathic nephrolithiasis.

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