Chapter 12

Genetic Predisposition in Kidney Stone Disease

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Abstract

Kidney stone disease (nephrolithiasis) affects approximately 10–15% of the global population and is now recognized as a chronic systemic condition with metabolic and cardiovascular implications. Its pathogenesis is multifactorial, involving genetic, metabolic, and environmental factors that drive urinary supersaturation and crystal formation. Heritability estimates of 45–55% underscore the substantial genetic contribution to individual susceptibility. The genetic architecture spans rare monogenic disorders — including primary hyperoxaluria, cystinuria, Dent disease, and Bartter syndrome — and common polygenic susceptibility identified through GWAS, implicating key loci such as CLDN14, SLC34A1, CASR, VDR, and CYP24A1. These variants disrupt fundamental mechanisms including hypercalciuria, hyperoxaluria, hyperuricosuria, reduced urinary citrate, and renal tubular dysfunction. Advances in next-generation sequencing have improved diagnostic precision and enabled genotype-guided management, while pharmacogenomics, RNA interference therapies, and microbiome–genetics interactions

offer emerging avenues for precision medicine. This chapter reviews the genetic basis of kidney stone disease — encompassing monogenic causes, polygenic risk, implicated pathways, and clinical implications — to inform personalized prevention and treatment strategies.

Keywords: Nephrolithiasis, genetic predisposition, monogenic disorders, GWAS, hypercalciuria, polygenic risk, precision medicine.

1. Introduction

Kidney stones, known in medical terms as nephrolithiasis or urolithiasis, are solid formations that develop in the kidneys from dissolved minerals found in urine. They signify a prevalent urological issue marked by the crystallization of minerals and salts in the kidney system.[1,2] The occurrence of kidney stones is rising globally, impacting around 10–15% of the world's population at some stage in their lives. The condition results in considerable suffering due to pain, urinary blockage, infection hazards, and possible kidney injury.[1]

Nephrolithiasis is a condition defined by the formation of solid crystal-like formations in the urinary region of the kidneys. There is significant diversity in its pathogenesis, risk factors, clinical development, and treatments.[2] Factors that increase the likelihood of people forming kidney stones can be genetic, metabolic, and environmental.[3,4] Nephrolithiasis is now recognized as a sign of systemic illness and a predictor of metabolic and cardiovascular problems.[10]

Systemic conditions, like problems with calcium balance, can increase the risk of developing kidney stones, and rare genetic factors leading to nephrolithiasis are widely recognized.[4] Nonetheless, most KSD cases are classified as idiopathic, with multiple genetic and environmental factors affecting the observed phenotype. The

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homeostatic and renal tubular mechanisms related to these common forms of kidney stone disease are not fully understood, which impedes efforts to develop improved treatment strategies to prevent kidney stone recurrence.[10,15]

Earlier genomic studies suggested that increased serum calcium and decreased serum phosphate levels are likely to heighten the risk of KSD, indicating that minor differences in mineral metabolism within the normal limits may function as a common risk factor for kidney stone formation.[15] As a result, a 0.08 mmol/L increase in serum calcium was linked to a KSD OR of 1.48, whereas a 0.16 mmol/L decrease in serum phosphate levels corresponded to a KSD OR of 1.41.[15] To improve our comprehension of how shifts in calcium and phosphate equilibrium contribute to kidney stone formation, research into genetic discoveries, laboratory experiments, and 3D modeling have been undertaken to pinpoint KSD-related variants associated with diacylglycerol kinase delta (DGKD), solute carrier family 34 member 1 (SLC34A1), and cytochrome P450 family 24 subfamily A member 1 (CYP24A1).[15]

2. Heritability of Kidney Stone Disease

Twin and family aggregation studies consistently demonstrate a significant hereditary component to kidney stone disease.[7,9] First-degree relatives of affected individuals face a markedly elevated risk of stone formation, reflecting familial clustering that points to genetic influence, though shared environmental factors may also contribute.[7] Monozygotic twins exhibit higher concordance rates than dizygotic twins, further supporting a heritable basis. Heritability estimates derived from epidemiological data range from 45% to 55%, indicating that genetic factors account for a substantial proportion of

individual susceptibility.[7] These findings underscore the importance of family history in risk assessment and highlight the need for genetic screening and early intervention in high-risk populations.[4,8]

3. Types of Kidney Stones and Their Genetic Basis

Kidney stones vary in chemical makeup and are categorized according to their chemical composition.[1,2] Stones that contain calcium are the most prevalent variety. Every type possesses unique genetic, biochemical, and clinical characteristics.[3,4]

3.1 Calcium oxalate stones

Calcium oxalate stones make up the largest portion of kidney stones, accounting for 70–80% of them, and usually have a polygenic origin, affected by various genetic variations and environmental influences.[3,4] Stone formation is affected by hypercalciuria, hyperoxaluria, low citrate levels in urine, and acidic urine pH. Genetic influences on calcium and oxalate metabolism are essential.[3,10] In a clinical setting, patients might show symptoms of repeated renal colic and blood in the urine.[1]

3.2 Calcium phosphate stones

Calcium phosphate stones can also develop, frequently forming on a calcium phosphate matrix referred to as Randall's plaque. They are infrequent, usually linked to alkaline urine and disorders such as renal tubular acidosis. Genetic variations influencing phosphate regulation and kidney acidification might play a role.

3.3 Uric acid stones

Uric acid stones are often associated with genetic elements affecting uric acid metabolism, including variations in the SLC2A9 (which encodes GLUT9) and ABCG2 genes. These stones develop in acidic

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urine and are linked to hyperuricemia, gout, and metabolic syndrome. Genetic susceptibility includes genes that control purine metabolism and kidney acidification. In a clinical setting, uric acid stones might not be visible on X-rays and need targeted diagnostic methods.

3.4 Cystine stones

Cystine stones serve as a typical illustration of monogenic kidney stone disorders, caused by mutations in the SLC3A1 and SLC7A9 genes that disrupt amino acid transport within the renal tubules. Cystinuria is a genetic disorder inherited in an autosomal recessive pattern, resulting from mutations in genes that code for renal amino acid transporters, causing reduced reabsorption of cystine and elevated cystine levels in urine. Cystine has low solubility, leading to frequent cystine stones. Cystine stones typically appear during childhood or adolescence and necessitate ongoing management throughout life.

3.5 Struvite stones

Struvite stones consist of magnesium ammonium phosphate and are mainly of infectious origin, linked to urinary tract infections caused by urease-producing bacteria. They are typically less associated with direct genetic predisposition, although host immune response genes may influence susceptibility.[1]

3.6 Rare Stone Types

Rare stone types include 2,8-dihydroxyadenine stones due to adenine phosphoribosyltransferase (APRT) deficiency and xanthine stones from xanthinuria, both having clear monogenic causes.[5,6] These disorders provide important insights into metabolic pathways of stone formation.[5]

4. Genetic Predisposition in Kidney Stone Disease

Genetic predisposition in kidney stone disease refers to inherited factors that increase an individual's susceptibility to forming stones.[4,13] The genetic factors influence essential body functions which include calcium metabolism and oxalate processing together with citrate excretion and renal tubular activity to create conditions that facilitate stone production. The familial clustering of kidney stones demonstrates that this condition has heritable characteristics.[7]

4.1 Familial Clustering and Heritability

Epidemiological studies show that first-degree relatives who have kidney stones face significantly higher chances of developing stones themselves.[7,9] The aggregation of this condition within families indicates a genetic basis although shared environmental factors might contribute as well. Twin studies demonstrate heritability because monozygotic twins show higher concordance rates than dizygotic twins.[7]

4.2 Gene Variants Affecting Metabolic Pathways

Calcium Transport Genes

The genes CLDN14 (claudin-14) and CaSR (calcium-sensing receptor) control the process of calcium reabsorption in the kidneys.[4,15] The presence of mutations or polymorphisms in these genes results in hypercalciuria, which causes excessive calcium loss through urine and represents a significant danger for developing calcium-based kidney stones.[4,10] The body loses control of calcium transport, which results in excessive calcium salt buildup in urine, leading to the development of crystal formation and expansion.[15]

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4.3.Oxalate Metabolism Genes

The AGXT gene, which encodes alanine-glyoxylate aminotransferase, contains variants that cause primary hyperoxaluria, a rare autosomal recessive disorder.[5,12] The condition results in higher production of oxalate within the body, which then leads to its excretion through urine, which creates a risk for developing calcium oxalate kidney stones.[5,6] The genes that control oxalate transport and metabolism pathways determine the likelihood of stone formation because they affect the amount of oxalate excreted through urine.[3]

4.4.Citrate Transport Genes

Citrate functions as a strong stone formation inhibitor because it binds with calcium to form chemical complexes.[1,10] The genetic changes that affect citrate transporter proteins result in decreased urinary citrate excretion which reduces the protective effects of citrate and raises the likelihood of stone formation.[4]

5. Monogenic (Mendelian) Disorders Causing Nephrolithiasis

The group of Mendelian disorders creates KSD, which develops in patients who experience their first symptoms during childhood and show severe disease progression.[5,6] The process of discovering these particular genetic factors establishes the foundation for precise diagnostic assessment and treatment planning.[12] The clinical presentation of these monogenic disorders starts in early life through recurrent stone formation and unique biochemical patterns which require genetic assessment for accurate diagnostic evaluation and treatment planning.[8,13]

5.1.Primary Hyperoxaluria

People who have this autosomal recessive disorder develop the condition because of genetic mutations which affect their AGXT (PH1) or GRHPR (PH2) or HOGA1 (PH3) genes. People who have this genetic disorder develop the condition because of an enzymatic defect which causes glyoxylate metabolism to fail. This defect results in their body making too much oxalate which leads to the development of severe calcium oxalate kidney stones.

5.2 Cystinuria

The condition occurs through autosomal recessive inheritance because of genetic variants which affect both SLC3A1 and SLC7A9. Patients who have this condition cannot properly absorb cystine along with dibasic amino acids because of genetic mutations which affect their ability to reabsorb these substances.

5.3 Dent Disease

The X-linked recessive disorder occurs through mutations which mainly damage CLCN5 and less often affect OCRL. The condition leads to patients experiencing low molecular weight proteinuria together with nephrocalcinosis and hypercalciuria and renal tubular dysfunction and nephrolithiasis.

5.4.Bartter Syndrome

The condition consists of a group of renal tubular disorders which follow autosomal recessive inheritance. The disorder causes patients to experience salt wasting and hypokalemia together with nephrocalcinosis and stone formation. The genes which have been mutated in this condition lead to changes in both kidney salt handling and calcium excretion processes.

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Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

The condition occurs through mutations which affect the CLDN16 and CLDN19 genes. These gene mutations lead to paracellular ion transport deficiencies in the kidney. The deficiency causes patients to lose both magnesium and calcium through their urine.

6. Polygenic Risk and Common Variants (GWAS Findings)

Genome-wide association studies (GWAS) have identified multiple susceptibility loci associated with KSD, including variants near CLDN14, SLC34A1, VDR, and CASR, highlighting the multifactorial nature of common nephrolithiasis.[15] The protective variant rs4293393-T near the UMOD gene, encoding uromodulin, has also been recognized.[16,17] Polygenic risk scores (PRS) derived from these variants offer promise for individual risk stratification and personalized prevention.[15] Furthermore, gene–environment interactions play a significant role, as genetic variants modulate individual responses to dietary and environmental factors in stone disease, including dietary consumption of calcium and oxalate, salt, hydration level, and daily habits, which demonstrate why customized healthcare needs complete solutions.[4,15]

7. The genetic basis of kidney stone formation

The genetic basis of kidney stone formation depends on multiple genes that collectively form pathways governing urinary solute concentrations.[4,15] The gene variants which control calcium transport through calcium-sensing receptor (CASR), vitamin D receptor (VDR), vitamin D 24-hydroxylase (CYP24A1), and sodium-phosphate cotransporters SLC34A1/A3 cause disruptions to calcium homeostasis which result in hypercalciuria.[14,15] SLC26A6 functions as an oxalate transporter while AGXT encodes alanine glyoxylate

aminotransferase which together act as vital controllers of oxalate processing and removal.[3,5] SLC2A9 (GLUT9) and ABCG2 together control uric acid transport through their effects on uric acid serum levels and renal excretion which establishes the connection between these factors and uric acid stone development.[15] The FGF23 axis works together with SLC34A1 to handle phosphate management because this system controls phosphate reabsorption and excretion while its disruption results in stone formation.[14] The proteins CLDN14, CLDN16, and TRPM6 function as essential magnesium transport proteins whose dysfunction increases the risk of kidney stone development.[5,15] SLC22A12 (URAT1) functions as a renal tubular transport protein that enables uric acid reabsorption throughout the kidney tubules.[15]

8. Role of Specific Genetic Variants

Kidney stone disease (KSD) develops from genetic variants which affect kidney function through two mechanisms: loss-of-function and gain-of-function effects that result in diminished or increased protein activity which subsequently affects stone development.[4,15] The CYP24A1 mutations which encode the enzyme that degrades 1,25-dihydroxyvitamin D lead to vitamin D inactivation impairment which results in idiopathic hypercalciuria and higher KSD risk.[15] Activating mutations in the calcium-sensing receptor (CASR) increase the body's excretion of calcium through urine which leads to increased kidney calcium levels and the development of kidney stones.[4,10] The common genetic variations found in CLDN14 function as one of the most important genetic risk factors that scientists have discovered for calcium stone disease.[15] The presence of a single SLC34A3 variant which causes hereditary hypophosphatemic rickets demonstrates

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that even one genetic change can increase an individual's chances of developing stone disease.[14]

9. Conclusion

The genetic components of kidney stone disease include three categories which are unique monogenic disorders and widespread polygenic risk factors and complex interactions between genes and environmental factors.[4,5,15] Genetic testing should become part of medical practice because it helps doctors make correct diagnoses and assess patient risk while creating tailored treatment plans which show how kidney stone disease has progressed from being seen as a urological condition to becoming recognized as a permanent systemic illness.[12,13] The field has made progress through GWAS discoveries and monogenic classification work yet fundamental knowledge gaps continue to exist about how common genetic variants increase disease risk.[15] The main research objectives will focus on conducting extensive genomic research and validating genetic variants through functional studies and connecting genomics with epigenomics and metabolomics and microbiome research to develop personalized medical treatments.[4,15]

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