Chapter 2

Impact of Monogenic Disorders and Calcium Metabolism Polymorphisms in Kidney Stone Disease

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Abstract

Kidney stone disease is a common urological disorder that affects nearly 10% of the global population. It is a multifactorial condition influenced by both genetic and metabolic factors. Disturbances in calcium metabolism play a major role in stone formation, and these metabolic processes are tightly regulated by various hormonal mechanisms. Genetic factors, particularly monogenic disorders and genetic polymorphisms, also contribute significantly to the development of kidney stones by altering calcium metabolism. Monogenic stone disorders arise due to inherited mutations in genes responsible for mineral metabolism and renal tubular transport in the kidney. Several inherited conditions, including Dent Disease, Cystinuria, and Primary Hyperoxaluria, are associated with recurrent stone formation.

In addition to these rare genetic mutations, genetic polymorphisms also influence susceptibility to kidney stone disease. Genetic

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polymorphism refers to the occurrence of common DNA sequence variation among individuals within a population. Variations in genes involved in calcium regulation, such as the Calcium-Sensing Receptor and the Vitamin D Receptor, play an important role in maintaining calcium homeostasis. Alterations in these genes may affect intestinal calcium absorption, renal calcium reabsorption, and overall calcium balance, thereby increasing the risk of calcium-based kidney stones.

This chapter provides an overview of calcium metabolism, the genetic basis of monogenic stone disorders, and the role of genetic polymorphisms in modulating calcium homeostasis. Understanding the interaction between hormonal regulation, genetic mutations, and polymorphic variations is essential for improving the diagnosis, prevention, and personalized management of hereditary kidney stone diseases.

Keywords: Monogenic Stone Disorder; Genetic Polymorphism; Dent Disease; Cystinuria; Primary Hyperoxaluria;

1. Introduction

Kidney stone disease is a prevalent disorder of the urinary tract characterized by the formation of crystalline mineral deposits within the renal collecting system as a result of supersaturation of solutes in urine. This condition, referred to as Nephrolithiasis, affects approximately 10% of the global population and its incidence has been increasing over the past few decades [1,2]. Clinically, patients often present with acute flank pain (renal colic), hematuria, and may also develop urinary tract infections or progressive deterioration of renal function in severe cases [3]. In addition, kidney stone disease is marked by a high recurrence rate, with nearly 50% of individuals

experiencing repeated stone episodes within a few years, thereby imposing a substantial burden on both patient quality of life and healthcare systems [4].

Kidney stone disease develops through a multifactorial process involving interactions between environmental influences, metabolic abnormalities, and genetic susceptibility [5]. Stone formation occurs when urinary solutes become supersaturated, leading to crystal nucleation, growth, and aggregation within the urinary tract [6]. Major stone-forming components include calcium, oxalate, phosphate, urate, and cystine, while substances such as citrate and magnesium act as natural inhibitors of crystallization [7]. Among these, calcium-based stones are the most common, underscoring the importance of disturbances in calcium metabolism in the development of nephrolithiasis [8]. Calcium balance in the body is regulated by coordinated renal and hormonal mechanisms involving key regulators such as Parathyroid Hormone and Vitamin D, which control intestinal absorption, bone resorption, and renal excretion of calcium [9].

In addition to metabolic factors, genetic influences play an important role in kidney stone susceptibility [10]. Some cases arise from monogenic disorders caused by mutations in single genes that affect renal tubular transport and mineral metabolism [11].Examples include Dent disease, cystinuria, and primary hyperoxaluria, which lead to abnormal urinary excretion of stone-forming substances and recurrent nephrolithiasis [12]. Advances in genomic technologies have enabled the identification of several genes responsible for these inherited conditions, improving diagnostic accuracy and understanding of their molecular mechanisms [13].

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Apart from rare monogenic mutations, common genetic variations also influence the risk of kidney stone formation. Genetic polymorphisms are naturally occurring DNA sequence variations that can affect gene expression or protein function [14]. Variations in genes involved in calcium metabolism, particularly the Calcium- Sensing Receptor and Vitamin D Receptor, may alter calcium absorption and renal handling, thereby contributing to stone susceptibility [15]. Understanding the combined effects of monogenic mutations and genetic polymorphisms is essential for clarifying the pathogenesis of nephrolithiasis and may support improved diagnosis, risk prediction, and personalized treatment strategies.

1.1. Monogenic Stone Disorder

Monogenic stone disorders represent a subgroup of kidney stone diseases that arise due to pathogenic variants in a single gene affecting renal tubular transport and mineral metabolism. These disorders typically follow patterns of Mendelian Inheritance, including autosomal dominant, autosomal recessive, or X-linked inheritance. In contrast to multifactorial nephrolithiasis, monogenic kidney stone disease is characterized by a strong genetic contribution and often presents with early onset, recurrent stone formation, and a positive family history. Genetic defects usually disrupt the renal handling of lithogenic substances such as calcium, phosphate, oxalate, or cystine, resulting in increased urinary excretion and subsequent crystal formation within the urinary tract.

Several well-characterized monogenic disorders are associated with kidney stone formation. Mutations in the genes SLC3A1 and SLC7A9 lead to Cystinuria, a disorder characterized by impaired renal reabsorption of cystine and dibasic amino acids, resulting in

excessive urinary cystine and recurrent cystine stone formation. Additionally, variants in genes involved in renal phosphate transport, including SLC34A1, SLC34A3, and SLC9A3R1, have been implicated in monogenic kidney stone disease through disruption of phosphate handling and mineral homeostasis. These transport defects increase the urinary concentration of crystallizing solutes, thereby promoting kidney stone formation [16].

1.2. Genomic Advances in the Diagnosis of Monogenic Nephrolithiasis

Advances in genomic technologies, particularly whole-exome sequencing, have enabled the identification of numerous genes associated with monogenic nephrolithiasis. Recent cohort studies demonstrate that rare pathogenic variants representing strong genetic risk factors are present in a subset of kidney stone patients, emphasizing the importance of integrating genetic testing with clinical and biochemical evaluation. Identification of such variants can facilitate more precise diagnosis, guide targeted therapeutic interventions, and enable genetic counseling for affected families.

Genetic testing is increasingly important for identifying inherited causes of kidney stone disease (KSD). Research indicates that nearly 15% of kidney stone cases seen in specialized clinics are linked to monogenic disorders resulting from mutations in a single gene. However, performing genetic testing for every patient is not feasible due to high costs and limited resources. As a result, careful selection of patients is necessary to ensure the effective use of genetic testing. Certain clinical characteristics—such as early onset of stone formation, presence of stones in both kidneys, nephrocalcinosis, and a family history of kidney stones—may suggest an underlying genetic

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cause. Patients with these features are therefore often prioritized for genetic evaluation. Recognizing these predictive clinical indicators can help clinicians identify individuals who are more likely to benefit from genetic testing, leading to improved diagnosis and more targeted management of hereditary kidney stone disorders [17].

2. Genetic Polymorphism

Genetic polymorphism refers to the presence of two or more variations in a DNA sequence within a population, where the least frequent allele occurs at a frequency of at least 1%. These variations arise through several biological processes, including mutations, errors during DNA replication, genetic recombination during meiosis, and exposure to environmental factors such as radiation or chemical agents. Although many polymorphisms are functionally neutral, some can alter important physiological pathways and contribute to differences in disease susceptibility among individuals. In particular, polymorphisms in genes involved in metabolic regulation, ion transport, and hormonal signaling may influence the risk of complex diseases such as kidney stone disease by affecting processes like calcium absorption, renal calcium reabsorption, and mineral metabolism [18] [19] [20].

2.1 Casr Gene Polymorphism in Kidney Stones

A case–control study investigated the relationship between polymorphisms in the calcium-sensing receptor (CaSR) gene and susceptibility to calcium-containing kidney stones in the Kunming Han Chinese population. The study included 100 patients with kidney stones and 100 healthy control individuals. Three CaSR gene polymorphisms—rs1042636, rs1801725, and rs1801726—were analyzed using SNaPshot genotyping technology. The findings

revealed that individuals carrying the rs1801725 GT genotype had a significantly higher risk of developing kidney stones compared with the control group. Moreover, these individuals exhibited increased 24-hour urinary calcium excretion, indicating reduced calcium reabsorption in the renal tubules. The elevated urinary calcium levels may contribute to the formation of calcium-based kidney stones [21].

2.2 Clinical Implications

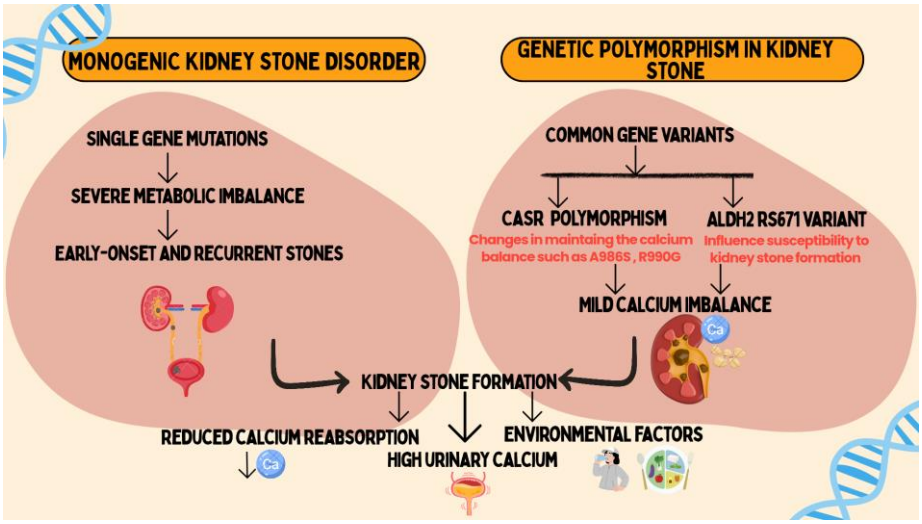

Figure 1: Genetic Basis of Kidney Stone Formation: Monogenic Disorders and Genetic Polymorphisms

Genetic variations, particularly single nucleotide polymorphisms (SNPs) in genes regulating calcium and phosphate transport or hormone signaling, can influence both the risk of kidney stone formation and responses to preventive treatments like thiazide diuretics and vitamin D–based therapies. Evidence from genome- wide association and Mendelian randomization studies suggests that genetic markers related to thiazide response are linked to lower stone risk, indicating that genotype may guide therapy [22]. Variants in calcium-sensing genes (e.g., DGKD), phosphate

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transporters (e.g., SLC34A1), and vitamin D metabolism genes (e.g., CYP24A1, VDR) are associated with changes in urinary calcium and phosphate handling, shedding light on the metabolic pathways underlying nephrolithiasis [23]. As genomic testing becomes more accessible, combining SNP data with biochemical profiles (e.g., urine calcium and citrate) and clinical history can support personalized kidney stone management through tailored surveillance and targeted interventions [24].

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