Asian Journal of Urology (2017) 4, 18–26

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

Review

The genetic framework for development of nephrolithiasis

Vinaya Vasudevan, Patrick Samson, Arthur D. Smith, Zeph Okeke*

Smith Institute for Urology, Hofstra Northwell School of Medicine, Lake Success, NY, USA

Received 7 July 2016; accepted 12 July 2016
Available online 28 November 2016

KEYWORDS
Genetics;
Hypercalciuria;
Nephrolithiasis;
Urolithiasis;
Calcium sensing receptor;
Cystinuria;
Medullary sponge kidney;
Autosomal dominant polcystic kidney disease;
Uric acid nephrolithiasis;
Hypercalciuria

Abstract Over 1%–15% of the population worldwide is affected by nephrolithiasis, which remains the most common and costly disease that urologists manage today. Identification of at-risk individuals remains a theoretical and technological challenge. The search for monogenic causes of stone disease has been largely unfruitful and a technological challenge; however, several candidate genes have been implicated in the development of nephrolithiasis. In this review, we will review current data on the genetic inheritance of stone disease, as well as investigate the evolving role of genetic analysis and counseling in the management of nephrolithiasis.

1. Introduction

Over 1%–15% of the population worldwide is affected by nephrolithiasis, which remains the most common and costly disease that urologists manage today. Identification of at-risk individuals remains a theoretical and technological challenge, as most patients who develop stone disease and subject to multiple environmental, geographic, and dietary exposures that could confound or increase the risk of developing stone disease. Establishing a genetic background for nephrolithiasis would better allow providers to

* Corresponding author.
E-mail address: ZOkeke@northwell.edu (Z. Okeke).
Peer review under responsibility of Second Military Medical University.

http://dx.doi.org/10.1016/j.ajur.2016.11.003

determine which individuals would require rigorous evaluation and screening, and may potentially alter the future of the management of stone disease. In this review, we will summarize the current data on the genetic inheritance of stone disease based upon urinary metabolic markers, and will also investigate implications of this research for the future management of nephrolithiasis.

2. Genetics of hypercalciuria

Approximately 75% of all stones are calcium-containing stones. Many theories have been discussed regarding which patients may be predisposed to calcium nephrolithiasis, with promising data discovered regarding specific mutations in different populations.

Primary hypercalciuria is a disorder characterized by altered calcium transport in the intestine, kidney, and bone with a 24-h calcium excretion exceeding 0.1 mmol/kg body in a morning urine collection. This phenomenon is typically seen in 40%—50% of adult patients and 10% of pediatric patients with nephrolithiasis. Current epidemiologic studies suggest that approximately 20% of patients with idiopathic hypercalciuria will report some family history of nephrolithiasis [1].

A strong case was previously made for autosomal dominant inheritance as the primary form of inheritance in idiopathic hypercalciuria. In several twin studies, monozygotic twins were shown to have a significantly higher concordance for hypercalciuria than dizygotic twins [2]. Moore et al. [3] had also observed primary hypercalciuria in 43% of all first degree relatives and 36% of all relatives of individuals with hypercalciuria in nine families, suggestive of an autosomal dominant pattern of inheritance, a finding corroborated by several other investigators [3—6]. Nicolaidou et al. [7] studied 40 children with hypercalciuria and 47.5% had a hypercalciuric first degree relative, 52.5% had sporadic disease.

However, critical epidemiologic analyses have found shortcomings in the theory of monogenic inheritance. In their landmark investigation, Resnick et al. [8] demonstrated that polygenic inheritance would be a more likely explanation. After interviewing 137 stone-forming patients, the author demonstrated that males were far more likely to develop nephrolithiasis; however, upon examining the possibility of X-linked, autosomal dominant, and autosomal recessive inheritance, he was unable to demonstrate a consistent relationship in his observations. He subsequently demonstrated that the risk of developing nephrolithiasis was significantly higher in the younger sibling of a patient diagnosed by calcium oxalate nephrolithiasis, there by establishing a polygenic means of inheritance. Overall, at least two or more gene loci were likely the culprit in all affected patients. Environmental factors, including dietary and geographic exposures, likely also played a role. In a twin study in Vietnam, Goldfarb et al. [9] later demonstrated that 56% of kidney stone susceptibility was attributable to genetic inheritance, while the other 44% could be explained by environmental factors. In several other studies, a codominant major gene model was found to account for heritability in over 50% of patients [10,11].

Since the advent of these discoveries, several genes have been implicated in the pathogenesis of hypercalciuria. We will review both animal and *in vivo* studies of these genetic aberrations.

2.1. Calcium sensing receptor

The calcium-sensing receptor (CaSR) is a plasma membrane G-protein coupled receptor found in the apical membrane of the nephron, the parathyroid gland, bone, intestine, and C-cells of the thyroid. Its function in the nephron is complex, and it is found in the proximal convoluted tubule, the thick ascending limb of the loop of Henle, the distal convoluted tubule, and the collecting duct [12]. It is regulated by extracellular calcium levels and controls parathyroid hormone (PTH) secretion and renal tubular calcium reabsorption. While its most commonly reported affiliation is with familial hypocalciuric hypercalcemia, it has also been implicated in heritable diseases of hypercalciuria and hypocalcemia.

Several single nucleotide polymorphisms (SNPs) have been examined in this patient population. One of the most studied polymorphisms involves the presence of two glycine residues at position 990, in place of one alanine seen in non-hypercalciuric patients. Replacement of Gly990 has been affiliated with hypercalciuria [13]. In one large retrospective review, 359 French-Canadian siblings with idiopathic hypercalciuria were found to have three SNPs on chromosome 3q13.3—21: Ala986Ser, Arg990Gly, Gln1011Glu (C-terminal, exon 7) [10]. Patients with primary hyperthyroidism were shown to more commonly express Arg990Gly polymorphisms, leading to higher calcium excretion rates.

Other polymorphisms identified include the Ala986Ser SNP and multiple SNPs within introns 1 and 4 found in the Chinese from Taiwan province and Italian populations, respectively [12].

2.2. Bicarbonate sensitive adenylate cyclase

The human soluble bicarbonate-sensitive adenylate cyclase (sAC) was identified as a highly significant locus involved in three families with hypercalciuria and nephrolithiasis. In a study of three families with absorptive hypercalciuria and nephrolithiasis, they were found to have linkage between a locus on the chromosome 1q23.3—24 and the absorptive hypercalciuria phenotype affiliated with the bicarbonate sensitive adenylate cyclase [14]. Of note, patients with severe hypercalciuria with an sAC mutation are more likely to have fasting hypercalciuria and osteopenia.

2.3. Vitamin D receptor polymorphisms

The vitamin D receptor (VDR) has been extensively investigated as a potential source of resorptive hypercalciuria. Its lithogenic potential has been demonstrated in rat models in which overexpression on intestinal epithelium increased hypercalciuria in stone-forming rats [15]. Most commonly, the *BsmI*, *Fok1*, *ApaI*, and *Taq1* polymorphisms are reliably associated with disruptions in vitamin D signaling aberrancies and calcium homeostasis. In the sentinel study on this mutation, six Indian families with