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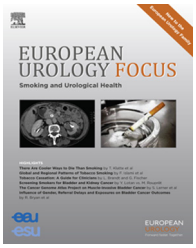

Review – Stone Disease

Genetic Risk Factors for Idiopathic Urolithiasis: A Systematic Review of the Literature and Causal Network Analysis

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Abstract

Context: Urolithiasis has a high prevalence and recurrence rate. Prevention is key to patient management, but risk stratification is challenging. In particular, genetic predisposition for urinary stones is not fully understood.
Objective: To review current evidence of potential causative genes for idiopathic urolithiasis and map their relationships to one another. This evidence is essential for future establishment of molecular targeted therapy.
Evidence acquisition: A systematic literature review from 2007 to 2017 was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines. The search was restricted to human studies conducted as either case–control or genome-wide association studies, and published in English. We also performed a causal network analysis of candidate genes gained from the systematic review using Ingenuity Pathway Analysis (IPA).
Evidence synthesis: During the systematic screening of literature, 30 papers were selected for the review. A total of 20 genes with 42 polymorphisms/variants were found to be associated with urolithiasis risk. Their functional roles were mainly categorized as stone matrix, calcium and phosphate regulation, urinary concentration and constitution, and inflammation/oxidative stress. IPA network analysis revealed that these genes connected via signaling pathways and a proinflammatory/oxidative environment.
Conclusions: This systematic review provides an updated gene list and novel causal networks for idiopathic urolithiasis risk. Although some genes such as *SPP1*, *CASR*, *VDR*, *CLDN14*, and *SLC34A1* were identified by several studies and recognized by prior reviews, further investigation elucidating their roles in stone formation will be essential for future studies.
Patient summary: In this review, we summarized recent literature regarding genes responsible for kidney stone risk. Based on a detailed review of 30 articles and computational network analysis, we concluded that disorder of mineral regulation with local inflammation in the kidney may cause kidney stone disease.

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1. Introduction

Urolithiasis has a high prevalence worldwide ranging between 7% and 13% in North America, 5% and 9% in Europe, and 1% and 5% in Asia [1]. Owing to the high recurrence rate of urolithiasis, both the American Urological Association [2] and European Association of Urology [3] recommend managing and preventing future recurrences by dietary and medical assessments. Single gene mutation states such as cystinuria are known to cause nephrolithiasis in a small proportion of stone patients [4]. However, in the large majority of patients who have idiopathic stone formation, less is known about contributing genetic factors. While numerous research efforts have been performed to elucidate the pathophysiology of lithogenesis [5], the exact mechanism of stone formation is still not fully understood.

Identifying genetic predisposition may lead to new prevention strategies for urolithiasis. For example, studies have demonstrated that a family history of urolithiasis increases relative risk by 2.57-fold in men [6]. In addition, the concordance rate of the disease in monozygotic twins is higher compared with that in dizygotic twins (32.4% vs 17.3%) [7]. These lines of evidence suggest that genetic factors for urolithiasis play a pivotal role in its etiology. By extension, elucidation of responsible genes could lead to future targeted gene therapy and better prevention.

Genome-wide association studies have widely been used for identifying genetic risk factors for various diseases. This approach facilitates examining entire DNA sequences to detect mutations, variants, and single-nucleotide polymorphisms (SNPs). SNPs play a crucial role in determining genes associated with urolithiasis that may serve as future diagnostic markers [8]. Understanding how these SNPs link together could potentially help unveil the genomic drivers of lithogenesis.

In this review, we focus on SNPs and genome-wide association studies (GWASs) conducted for urolithiasis. We present a systematic review of genetic risk factors for stone formation and a network analysis of candidate genes. Our aim is to provide an update on genes associated with nephrolithiasis and how they may interact with one another.

2. Evidence acquisition

We performed a systematic literature review in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines [9]. In PubMed and Medline databases, the following search keywords were used: ((“genome”[MeSH]) OR (“mutation”[MeSH]) OR (“genetic”[MeSH]) OR (“single nucleotide polymorphism”[MeSH])) AND ((“urolithiasis”[MeSH]) OR (“nephrolithiasis”[MeSH]) OR (“kidney calculi”[MeSH]) OR (“urinary calculi”[MeSH]) OR (“calcium oxalate”[MeSH]) OR (“calcium phosphate”[MeSH]) OR (“uric acid”[MeSH])). The search was restricted to human studies with both an abstract and the full text available; published in English during the last 10 yr. Studies were considered only if patient cases were confirmed as having either renal or ureteral stones diagnosed previously. A total of 237 papers were reviewed; 54 case reports and 33 reviews were excluded. Cohort studies; negative studies; and studies irrelevant to urolithiasis and nephrolithiasis were screened. After exclusions; 30 papers were selected for this review (Fig. 1).

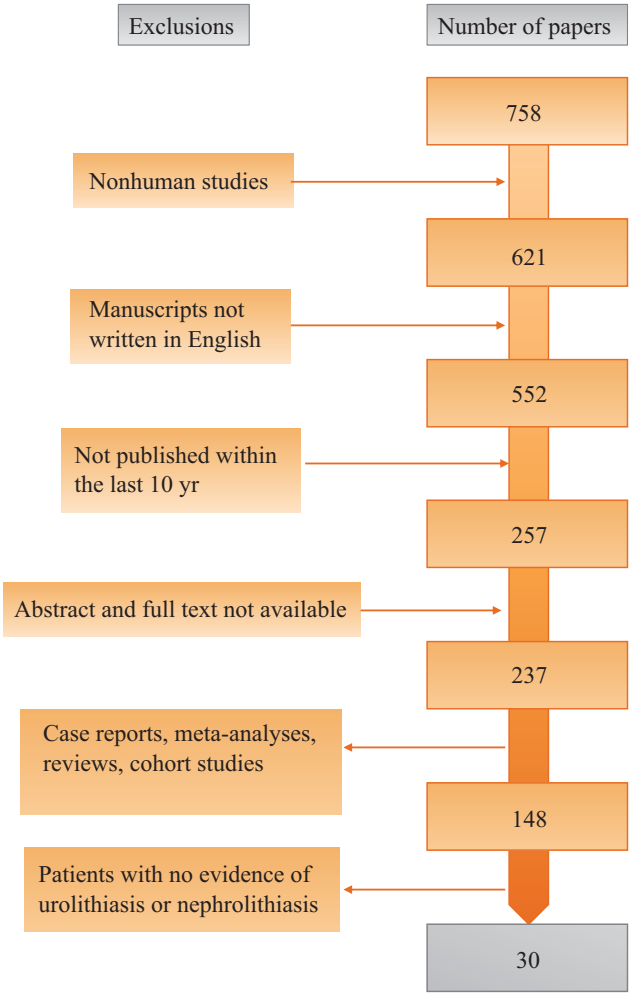

Fig. 1 – Flow chart of the methods used to formulate this systematic literature review in accordance with PRISMA guidelines.
PRISMA = Preferred Reporting Items for Systematic Review and Meta-analyses.

Existing networks among candidate genes for urolithiasis development were also analyzed. Ingenuity Pathway Analysis (IPA; QIAGEN, Hilden, Germany) uses computerized analysis with a mega knowledge base of reviewed scientific literature [10]. The use of IPA methodology allowed a causal network analysis for the candidate genes.

3. Evidence synthesis

From the selected 30 papers, 20 genes were identified with 42 SNPs/variants reported in case–control and/or GWASs. Most investigations consisted of Asian and European patients. Table 1 summarizes the genes associated with urolithiasis risk factors. The majority of genes were