UNDERSTANDING THE CLINICAL GENETICS OF KIDNEY STONE DISEASE USING THE NATERA® RENASIGHT™ PANEL

INTRODUCTION

Although the etiology of kidney stone disease is multifactorial, emerging evidence suggests that genetically-linked kidney stone disorders are much more prevalent than previously realized.[1] Some studies have shown at least an 11% population incidence of monogenetic stone-causing mutations, while others have suggested that heritability accounts for 45% to 56% of kidney stone prevalence.[2-4] Precision medicine approaches to kidney stone disease detection and management, including genetic studies and genome-wide association studies, are generally cost prohibitive and unavailable. In this study, we aimed to better understand the most common underlying genetic causes of kidney stone formation using a new kidney disease-focused genetic test, the Natera® Renasight™ panel.

METHODS

We conducted an IRB-approved observational prospective study of the Natera® Renasight™ panel of patients at high risk for stone formation at a diverse, urban academic center. Patients who had a personal history of recurrent kidney stones (≥ 2 episodes) or a personal history of stones with a family history of stone formation were asked to participate in the study. Patients on stone-forming medications or with known genetic causes of stones, anatomical abnormalities, acute UTI, and acute stone passage episodes were excluded. Cheek swabs were used to collect DNA samples for further genetic analysis. All patients also underwent standard-of-care metabolic evaluation with bloodwork and 24-hour urine studies using Litholink. Patient information including demographics, medical history, and stone characteristics and history was collected through retrospective chart review. Descriptive statistics were performed using SPSS.

RESULTS

A total of 28 patients were enrolled in the study, 18 (64.3%) of whom were women. Five (17.9%) were non-Hispanic white, three (10.7%) were non-Hispanic black, three (10.7%) were Asian, and 13 (46.4%) were Hispanic. The average age was 49 (IQR 32-60) years, and the mean BMI was 30.9 (IQR 25.8-36.9). Ten (35.7%) patients had hypertension and 8 patients had diabetes (28.6%). Three (10.7%) patients were former or active smokers and five (17.9%) reported alcohol use.

The mean number of stone episodes in the last 5 years was 2 (IQR 1-3), and the more than half (53.6%) of patients were treated with ureteroscopy. The most common type of stone was calcium oxalate (39.3%) followed by a mixed type (17.9%); the average size of the most recent stone was 5 mm (IQR 2-10). Nine (32.1%) patients reported having a first-degree family history of kidney stone disease. Litholink studies were unremarkable except for a mean urine citrate of 369 (IQR 212-660).

Two (8.3%) patients were positive (*TTR* and *COL4A3*) and 11 (45.8%) were carriers for genes that have been studied for hereditary stone disease. 128 variants of unknown significance (VUS) were detected; the most commonly affected genes were *PKD1* (5), followed by *CEP164*, *MEFV*, and *RPGRIP1L* (4). The detected VUS predisposed patients most commonly to different nephronophthisis phenotypes (37.5%), followed by polycystic kidney disease (33.3%), Senior-Loken syndrome (29.2%), and Fanconi anemia (25%).

CONCLUSION

Our study provides a comprehensive descriptive analysis of demographics, stone history, and genetic findings in patients at high risk or having a family history of stone formation using a genetic test that could become a relatively affordable and available option for patients. Our initial wide range of genetic results supports hypotheses that hereditary causes of stone disease are likely polygenetic, and its phenotypes result from a complex interplay of several genetic and non-genetic factors.

1. Howles SA, Thakker RV. Genetics of kidney stone disease. *Nat Rev Urol*. Jul 2020;17(7):407-421. doi:10.1038/s41585-020-0332-x
2. Halbritter J, Baum M, Hynes AM, et al. Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. *J Am Soc Nephrol*. Mar 2015;26(3):543-51. doi:10.1681/asn.2014040388
3. Goldfarb DS. The search for monogenic causes of kidney stones. *J Am Soc Nephrol*. Mar 2015;26(3):507-10. doi:10.1681/asn.2014090847
4. Goldfarb DS, Fischer ME, Keich Y, Goldberg J. A twin study of genetic and dietary influences on nephrolithiasis: a report from the Vietnam Era Twin (VET) Registry. *Kidney Int*. Mar 2005;67(3):1053-61. doi:10.1111/j.1523-1755.2005.00170.x