Next-generation sequencing in nephrolithiasis/nephrocalcinosis

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Nephrolithiasis (NL) is less common in children but often indicates underlying metabolic conditions or anatomical abnormalities [1]. More than 40% of the children with NL would have some identifiable metabolic predisposition [1,2]. Nevertheless, infection as etiology of NL should be considered in cases of struvite calculi [2].

Nephrocalcinosis (NC) on another hand is the deposition of calcium in the parenchyma and tubules [3]. Based on the position of involvement, NC is divided into medullary and cortical NC [4]. Medullary NC is more common and seen in 97% of the cases with remaining 3% of cases accounting for cortical NC, which occurs due to underlying cortical disease such as renal cortical necrosis. Several genetic disorders have been found to be associated with NC, chiefly being renal tubular disorders associated with cellular and paracellular ion transport disorders leading to higher levels of calcium, phosphate or oxalate, and lower levels of citrate and magnesium [4].

In this issue of Indian Journal of Child Health, Saha *et al*. [5] published their study conducted on 13 children with NL/NC utilizing next-generation sequencing (NGS) method covering 8882 genes. A total of eight children had NC, seven had NL, and seven children presented as end-stage renal disease. Of 13 children, 11 children had identifiable genetic cause of NC/NL, primary hyperoxaluria (PH) type 1 being the most common condition identified in 6 patients, Lesch Nyhan syndrome in 2, PH type 2, PH 3, and FHHNC in 1 each patient.

Although the study provides preliminary NGS data in Indian children with NL or NC, the report has some limitations, the major being small sample size, retrospective nature of the study, and incomplete use of the American College of Medical Genetics (ACMG) classification guidelines [6]. ACMG recommends classification of variants into the five categories based on evidence from population allele frequencies, predictions from *in silico* tools, segregation data, and functional validation. Despite the availability of Indian origin population level whole genome sequencing datasets [7], the frequency of these alleles has not been investigated. Indian genome sequencing consortium [8] datasets provide an even greater sampling of Indian populations and would be an extremely valuable addition to the interpretation of the data. Although the variants are described based on the functional consequence to the amino acid sequence, it would have been noteworthy, if authors would have performed *in silico* predictions. Several well-established *in silico* tools that rely on evolutionary conservation and protein structure are routinely used to better characterize the impact of mutations. Given the small sample size used in the study, the authors could have easily investigated the segregation data in greater detail across multiple generations to obtain stronger support for the associations identified. None of the candidates identified are functionally validated using *in vitro* and animal model studies.

There is a paucity of data exploring the inherited cause of NC/NL from India. Ramya *et al*. [9] studied 54 children with NC and reported distal renal tubular acidosis (RTA) followed by PH as the common etiology based on biochemical studies. However, genetic confirmation was sought in only eight patients which was one of the major limitations of this study. Another study from North India studied 40 children with NC and reported distal RTA as the most common etiology (50%) followed by idiopathic hypercalciuria (7.5%) and hyperoxaluria (7.5%) based on biochemical parameters only [10]. Future studies should focus on evaluating all the AMCG criteria and providing candidates that can be functionally validates to establish causality.

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