

# Monogenic Nephrolithiasis—Collision of Phenotypes, Genotypes, and Phenocopies



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Kidney stone disease is not uncommon in the general population and can be underpinned by multiple potential and predisposing underlying biochemical phenomena and phenotypes.<sup>1</sup> The unraveling of these phenotypes and their potential monogenic and polygenic relationships<sup>2</sup> is revealing a much more complex landscape than was previously appreciated. Even for the most significant of major underpinning urinary phenotypes, such as hypercalciuria,<sup>3</sup> this is revealing complexity even though pathways toward precision medicine for affected individuals are being conceptualized.<sup>4</sup>

Cogal *et al.*<sup>5</sup> report in this issue significant insights into phenocopy phenomena at scale within substantial cohorts of several kidney stone diseases which classically have clear phenotypes and

monogenic relationships, specifically Dent disease (DD) and primary hyperoxaluria (PH). Interestingly, a significant minority of cases in both instances that did not have an identifiable underlying monogenic cause in the known genes for DD or PH were found to be underpinned by pathogenic variants in genes classically related to other specific kidney stone disorders. Of important clinical relevance at this juncture where genomics is increasingly transitioning into the clinic and mainstream clinical practice, this was identified by applying clinical variant classification reporting criteria (American College of Medical Genetics) and using sequencing technologies that are readily available and relevant. Cases of both DD and PH were well phenotyped within the context of clinicians who are experienced in doing so for rare forms of nephrolithiasis, specifically those within the Rare Kidney Stone Consortium. Even in spite of these efforts that might otherwise make one think that such cases would be less likely to be due to bona fide

phenocopy presentations of other kidney stone disorders, that is what was revealed in approximately 1 in 10 DD cases and 1 in 4 PH cases in whom results of genetic testing of known DD and PH genes had previously returned negative.

So, where to from here? Does this indicate that phenotyping in kidney stone disease is increasingly superfluous and destined to be replaced by genomic testing? In short, no. This rather indicates that there is emerging a more nuanced and pragmatic nexus between detailed clinical phenotyping and potential application of genetic testing to arrive at a precise kidney stone disease diagnosis for affected patients and families. It is important to note that there are instances in which detailed phenotyping may provide information that is critical for the accurate curation of some genetic variants and which may alternatively have not resulted in a positive diagnosis in the absence of such phenotyping. In this publication,<sup>5</sup> these are unlikely to have been included in the particular DD and PH cohorts reported as they would instead have previously had a positive genetic diagnosis. Conversely, it is likely the juxtaposition of the precise phenotypic features in the reported instances of DD and PH related to pathogenic variants in alternate kidney stone disease genes that provides interesting and informative insights. It certainly indicates that even within the spectrum of kidney stone disease, there is a complex interplay between kidney physiology, genetic variation, and disease states that might all lead to a common final pathway of a patient presenting with nephrolithiasis.

One critical value of this publication from Cogal *et al.*<sup>5</sup> is

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the detailed demonstration of utility and phenocopy instances at a scale that is generalizable for clinical practice. Similar findings have been identified in a research genomics context in preceding studies<sup>6–9</sup> across international cohorts of adults and children affected by kidney stone disease. These preceding studies have been critical to set the scene for translation and have directed critically needed attention toward nephrolithiasis as a condition that is of significant global prevalence and morbidity. They also set the scene to reveal diagnostic complexity that has been significantly advanced with the application of genomics at this intersection of nephrology and urology. The findings of a significant genetic diagnosis rate and unappreciated underlying genetic diagnoses, which may have specific relevance to personalized treatment, have laid the foundation for the work of the Rare Kidney Stone Consortium to now reveal how the next iteration as genomics for kidney stone disease moves significantly closer to the clinical mainstream.

Another key point is how Cogal *et al.*<sup>5</sup> have further reinforced previous general observations across the rare and genetic disease space that specific features can increase the likelihood of identifying a monogenic diagnosis. These include younger age of disease onset, positive family history, and consanguinity. For clinicians, confirmation that these clinical features continue to have applicability in identifying monogenic forms of kidney stone disease is both reassuring and useful. It is not however the whole story, as it is also clearly revealed that there are cases among whom a genetic diagnosis may very well be present

in the absence of such supportive or apparently indicative features. Moving forward, this increasing body of evidence<sup>5–9</sup> gives opportunity to reflect on key principles and approaches for integration of clinical genomics in the assessment and evaluation of kidney stone disease.

At this time, it remains clear that clinical phenotyping is a mainstay of evaluation for cases of potentially monogenic kidney stone disease, especially those with recurrent presentations, a positive family history, younger age of onset, or specific additional features, such as low molecular weight proteinuria or nephrocalcinosis. In fact, several of those features may only be revealed by scratching the surface of assessment or history taking a little deeper, and this may in fact provide the greatest clinical utility of all for case identification. One line of inquiry for future exploration is as to how to best integrate such case identification into primary, acute, or emergency care settings where patients might present with a first or subsequent presentation of acute nephrolithiasis or its complications.

Phenotype-informed clinical genomic testing now also very much has a definable role in kidney stone disease assessment, and its utility both diagnostically and more broadly in regard to potential therapies is growing. There are now definable circumstances where not only can such clinical genomic approaches confirm a clinical diagnosis and have implications for treatment and approach to at-risk family members but also a somewhat unexpected alternate phenocopy diagnosis may be revealed. Although clearly the minority of instances, they are no less important and may advance meaningfully collective progress toward precision diagnosis in

nephrolithiasis, especially within this more nuanced scene of phenotype, genotype, and phenocopy phenomena.

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## Author Contributions

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