Diagnostic Yield and Clinical Utility of Nephrolithiasis and Primary Hyperoxaluaria Sequencing panels

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Introduction

- Nephrolithiasis (so called kidney stones, renal calculi or urolithiasis) is one of the most common renal complications with more than 200,000 cases diagnosed in the US every year.
- The etiology of nephrolithiasis is multifactorial involving both genetic and environmental factors.
- Half of all affected individuals have a family history of kidney stones suggesting the genetic trait plays a vital role in disease manifestation.
- PKIG designed a 35-gene Nephrolithiasis and a 3-gene Primary Hyperoxaluaria gene panels to identify the genetic underlining of these diseases

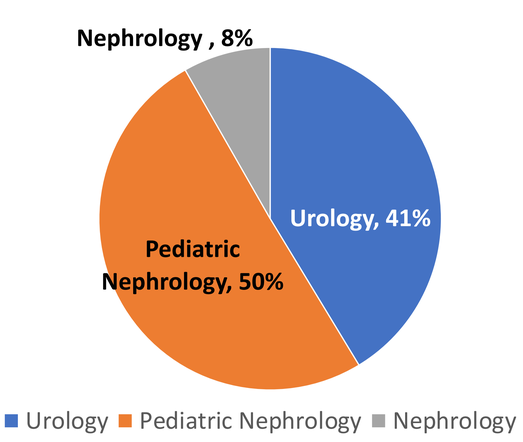
Methods

- In total 121 samples between June 2020 and February 2022 were tested at our laboratory.
- Sample types includes dried blood spot (DBS), saliva swab, and whole blood
- Samples came from three different types of clinics
    - Urology
    - Nephrology
    - Pediatric nephrology
- There are 55% males and 45% females.
- Next generation sequencing and deletion/duplication analysis were performed using a capture-based library on Illumina sequencer.

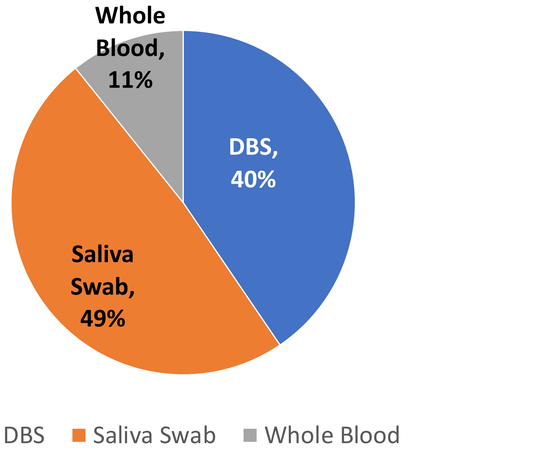
RESULTS

- A diagnosis was reached in 15% of these cases (24 cases) with equal split between Nephrolithiasis and Primary Hyperoxaluaria gene panels.
- Diagnostic findings for Primary Hyperoxaluaria panel were all due to homozygous or compound heterozygous pathogenic variants in the AGXT gene.
- Diagnostic findings for the nephrolithiasis panels:
    - The majority were identified with biallelic pathogenic variants in autosomal recessive genes: *GRHPR, ATP6V0A4, SLC7A9, CLDN16 and ATP6V1B1*
    - One X-linked gene *CLCN5*
    - One autosomal dominant gene *CASR*
- All disease-causing variants detected have been reported in literature previously, supporting that genetic underpinnings play an important role in the etiology of kidney stones.
- Potential diagnostic findings:
    - An additional 6% cases (7 total) with variant(s) of uncertain significance that may potentially become diagnostic based on inheritance. Among these, half are autosomal recessive and half are autosomal dominant.
    - There are 2% cases (2 total) with pathogenic/likely pathogenic variant(s) in genes that have been reported as both autosomal dominant and autosomal recessive inheritance.
    - Familial segregation studies would be the next step to further investigate the potential pathogenicity of these variants and/or diagnosis of disease.

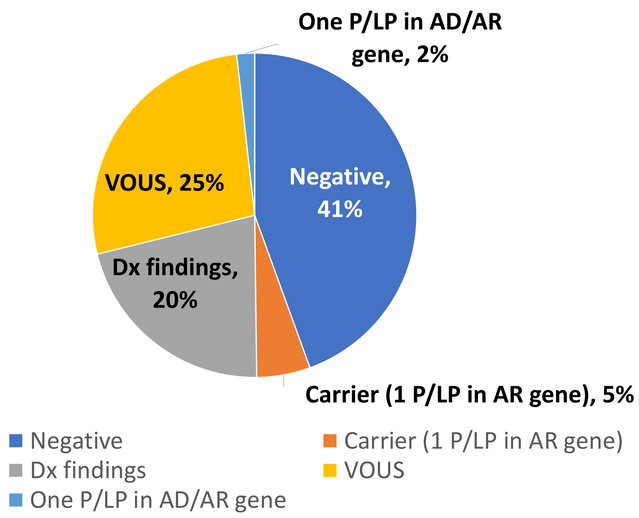
Client practice category



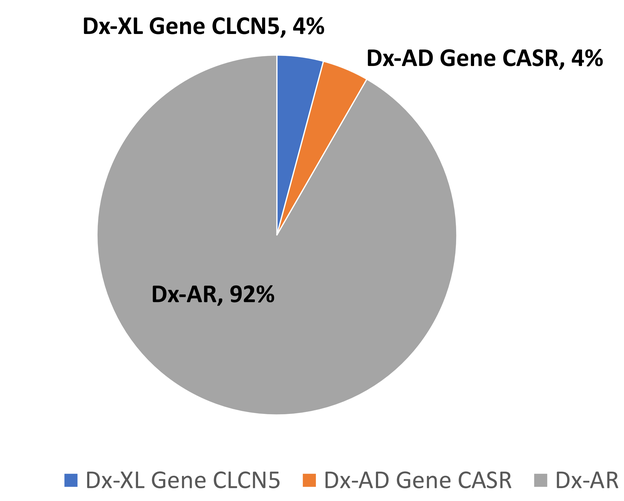
Sample type distribution



Sequencing results/variant types



Inheritance of diagnostic findings



CONCLUSION

- Our 35-gene Nephrolithiasis and 3-gene Primary Hyperoxaluaria sequencing panels have a high diagnostic yield with significant potential for clinical use.
- Given the prevalence of genetic causes in these diseases, gene sequencing should be considered as first line testing and standard of care.
- Familial segregation study is the next step to reach possible diagnosis for those identified with variant(s) of uncertain significance or one pathogenic/likely pathogenic variant with uncertain inheritance.

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