

Findings from next-generation sequencing-based multi-gene panel testing for individuals with nephrolithiasis

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Introduction

- Nephrolithiasis, or kidney stone disease, affects ~9% of the population in the United States.¹
- Treatment of nephrolithiasis can be guided by understanding the molecular pathway involved. Genetic testing can be a helpful tool with biochemical testing to confirm the precise diagnosis.
- In this study, we assessed the utility of next-generation sequencing (NGS) multi-gene panel tests for individuals with suspected nephrolithiasis with an overview of genetic findings identified in this population.

Methods

- The study consisted of a retrospective review of clinical reports for 160 patients with an indication of nephrolithiasis who underwent panel testing at Blueprint Genetics.
- Panel testing included both sequence and copy number variant (CNV) analyses of NGS data from validated assays. The target region included the coding exons (+/- 20 bp from the intron/exon boundary) of up to 45 genes associated with nephrolithiasis. CNV analysis was performed bioinformatically from NGS data using 2 variant-calling algorithms, including a proprietary method specific for small, exon-level CNVs.

Results

- The median patient age at time of testing was 14 years (range, 3 months to 77 years). The cohort was 56.9% (91/160) males.
- A positive result was reported in 21.9% of patients (35/160) (Figure 2a) across 14 genes, with *CYP24A1* associated with autosomal recessive hypercalcemia/hypercalciuria (n=7) and *SLC7A9* associated with autosomal dominant and recessive forms of cystinuria (n=6) being the most frequent (Figure 1).
 - For this study, a positive result was defined as the identification of pathogenic or likely pathogenic variant(s) consistent with the patient's reported phenotype and with known associated disease inheritance.
 - Variant interpretation and reporting were performed using modified ACMG/AMP guidelines.
- Genes associated with hypercalciuric nephrolithiasis (*CASR*, *CLCN5*, *CLCNKB*, *CLDN16*, *CYP24A1*, *SLC12A1*, *SLC34A1*) accounted for almost half of positive results (54.3%, 19/35).
- Almost all variants contributing to positive results were sequence variants (97.9%, 47/48), apart from a pathogenic 21kb deletion of exons 1-3 of the *CLCNKB* gene identified in trans with a hemizygous likely pathogenic frameshift variant, c.38_59delinsAGTCAC p.(Gly13Glufs*22), which is associated with autosomal recessive Bartter syndrome (Figure 2b).

Conclusion



One in 5 patients undergoing next generation sequencing (NGS) panel testing for the indication of nephrolithiasis had a molecular finding supporting the diagnosis.

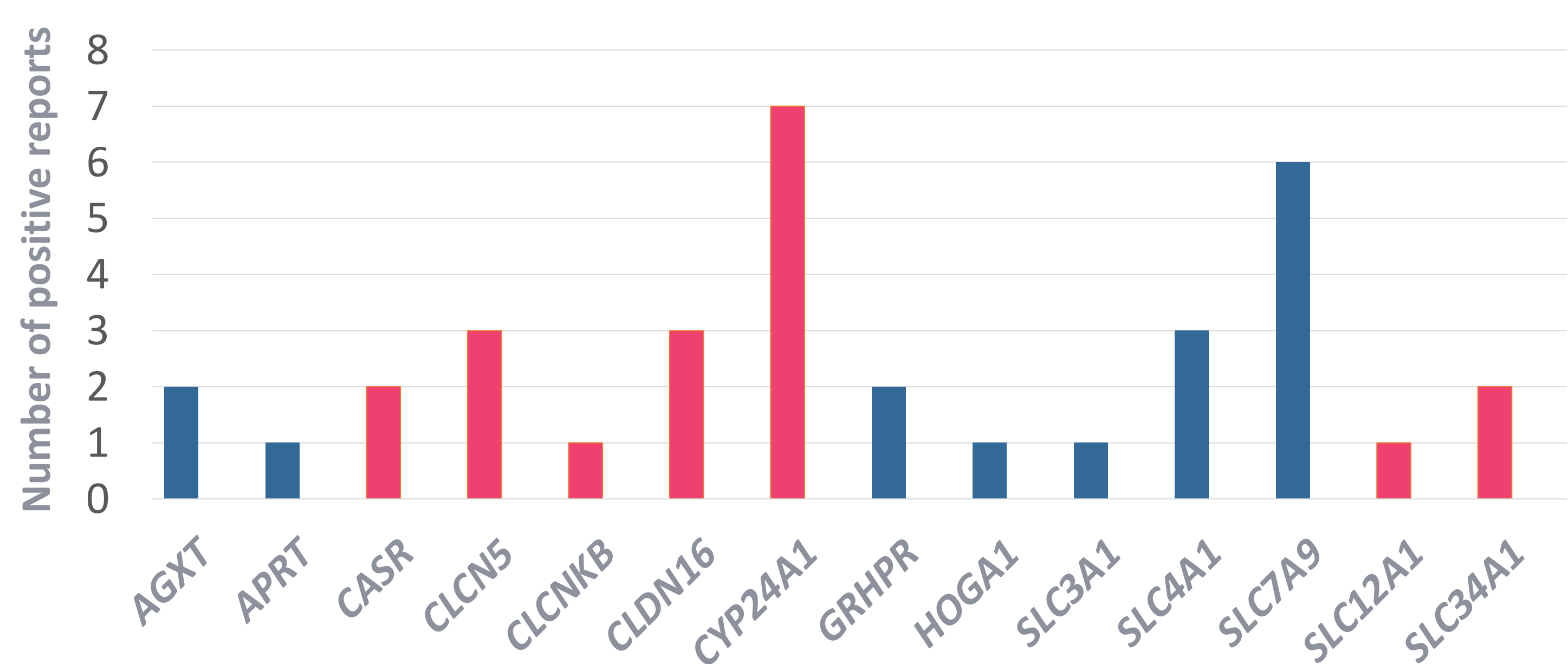


Figure 1. Frequency of genes with positive findings. Genes associated with hypercalciuric nephrolithiasis, accounting for almost half of positive results (54.3%, 19/35), are in pink and others are in blue.

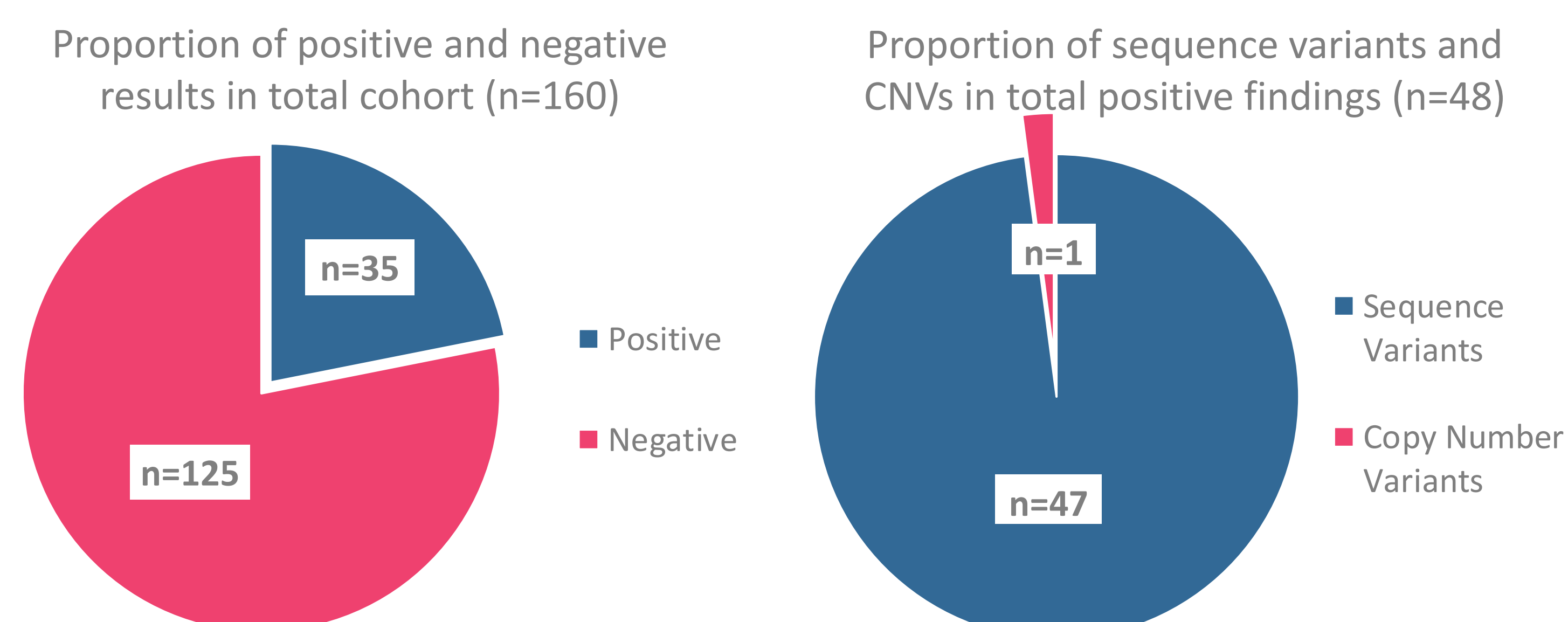


Figure 2. Characterization of positive results: (a) Proportion of positive and negative results in total cohort; (b) Proportion of sequence variants and copy number variants in total positive findings.