

Genetic insights into cystic kidney diseases: phenocopy detection through next-generation sequencing



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INTRODUCTION

Cystic kidney diseases represent a group of genetically heterogeneous disorders with pathogenic variants in *PKD1* and *PKD2* genes being the most common (about 94%) cause of autosomal dominant polycystic kidney disease (ADPKD) [1]. While clinical diagnosis can often be easily made upon clinical imaging criteria, the implications of next-generation sequencing not only allow to investigate the structurally complex *PKD1* gene and confirm a diagnosis, but also unveiled the existence of various phenocopies [2].

AIM

To identify and classify genetic variations within kidney-associated genes among patients presenting with multiple renal cysts, with a particular focus on detecting non-*PKD1/2* genetic causes.

MATERIALS AND METHODS

The study group: 76 patients with multiple renal cysts (43 females and 33 males; 69 adults and 7 children)

Kidney-focused next-generation sequencing panel of 498 genes (including *PKD1*, *PKD2*, *PKHD1*, *ALG5*, *DZIP1L*, *DNAJB11*, *GANAB*)

Assessment of detected variants pathogenicity using the American College of Medical Genetics and Genomics guidelines.

Pathogenic/likely pathogenic variants and variants of uncertain significance (VUS) were reported (n = 61)

Phenotype-related variants were identified in 61 patients (80%) (Supplementary data). The most frequently involved genes were *PKD1* (40 patients, 66%) and *PKD2* (11 patients, 18%) (Figure 1).

In *PKD1* gene 32 variants were classified as pathogenic/likely pathogenic, and 8 as VUS (Figure 2). 22 variants were not described in the literature (Figure 3).

The remaining variants were detected in non-*PKD1/2* genes: *COL4A5*, *PAX2*, *COL4A1*, *PKHD1*, *NPHP1*, *GANAB*, *HNF1B*, and *UMOD*. In these cases, two patients were clinically diagnosed with ADPKD, so the existence of phenocopies was observed in our study.



Supplementary data

RESULTS

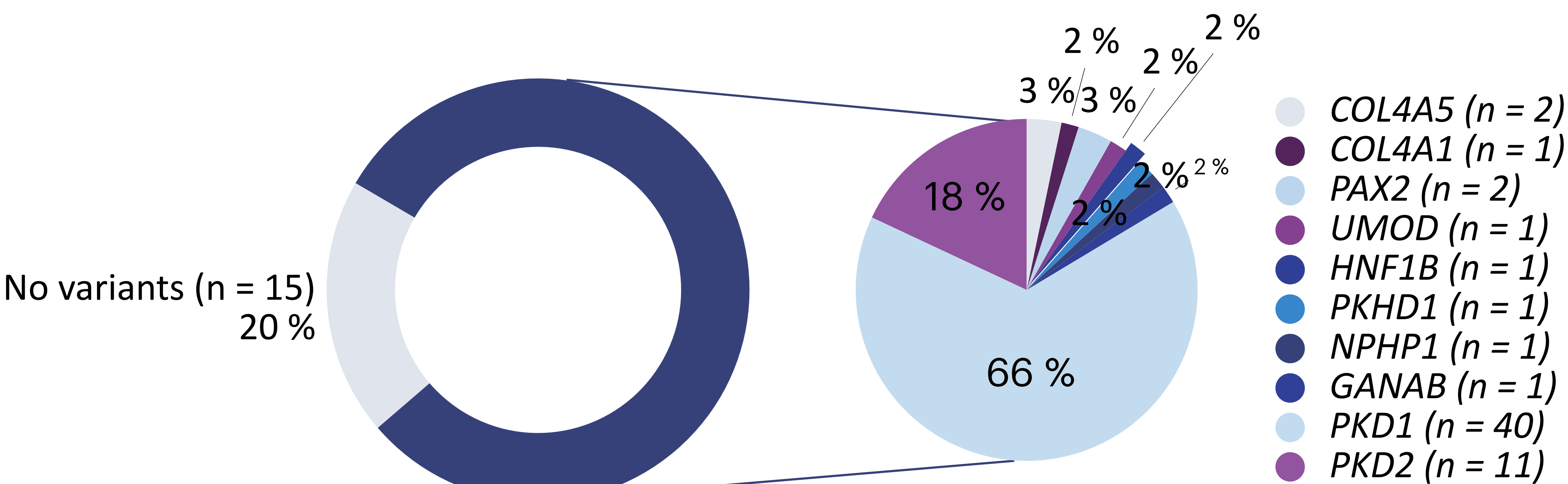


Figure 1. Distribution of genes in the study group.

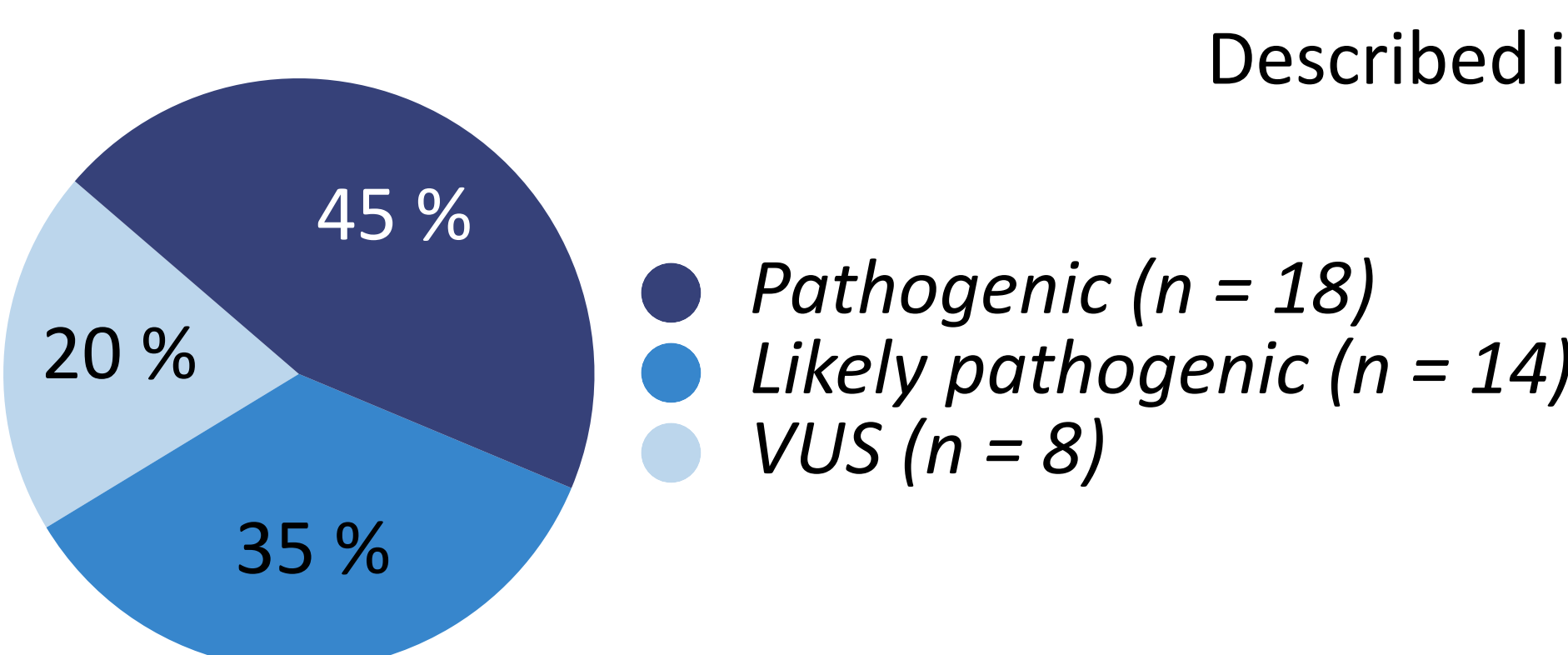


Figure 2. Pathogenicity of variants in *PKD1* gene.

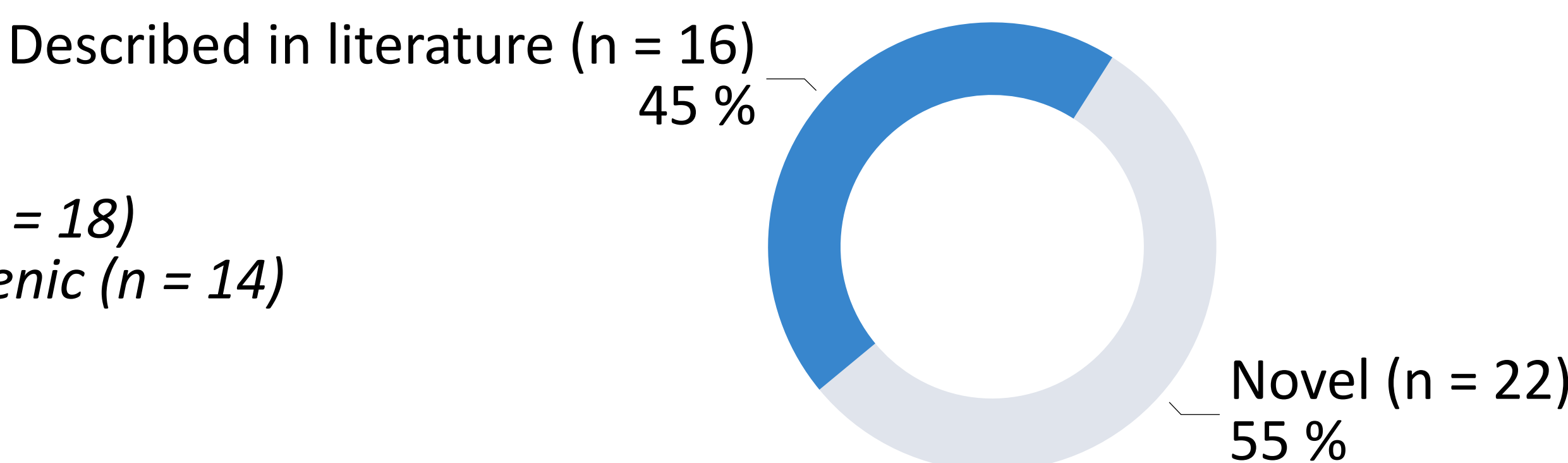


Figure 3. Novelty of *PKD1* variants.

DISCUSSION AND CONCLUSION

The high variant detection rate among patients with cystic kidney disease reflects results similar to those of other studies worldwide [2, 3], and a genetic diagnosis was established for the majority of patients in our study. As imaging criteria for the diagnosis of ADPKD were developed before the identification of additional dominant PKD genes such as *GANAB*, *ALG8*, *ALG9*, *LRP5*, and *DNAJB11*, they do not reliably apply to these disorders and may require reevaluation [2]. Previously undescribed novel variants were identified in our study. As expected, some non-*PKD1/2* patients demonstrated phenotypes resembling or identical to classic ADPKD. Patients, genetic confirmation is the basis of personalised patient care and bears significant midterm to long-term prognostic value.

REFERENCES

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